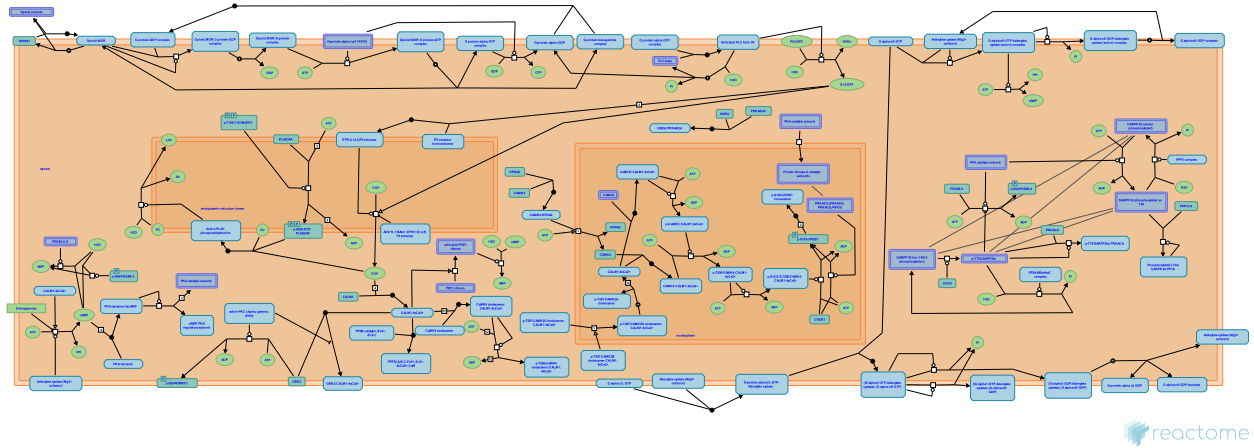


Opioid Signalling



Castagnoli, L., Jassal, B., Le Novere, N., Schmidt, EE.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook).

25/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

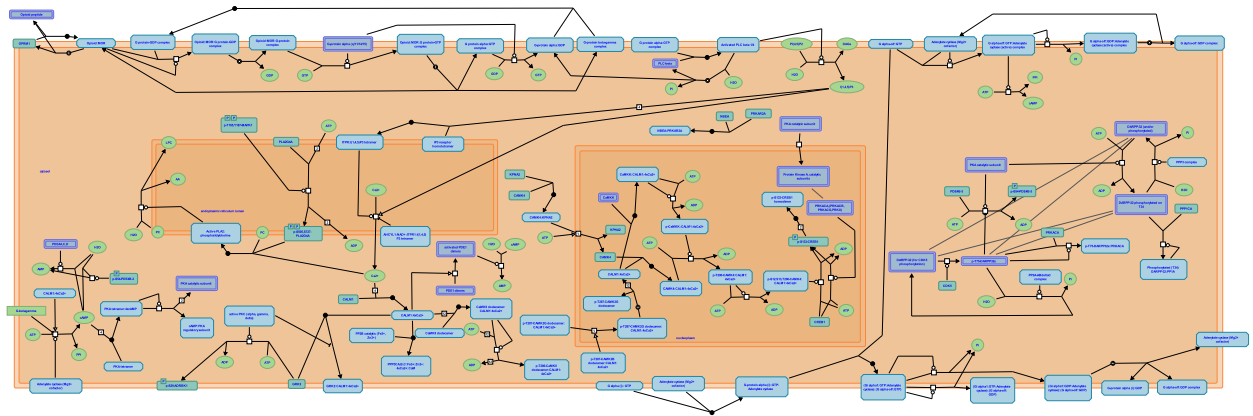
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Reactome database release: 88

This document contains 4 pathways and 2 reactions ([see Table of Contents](#))

Opioid Signalling ↗

Stable identifier: R-HSA-111885



reactome

Opioids are chemical substances similar to opiates, the active substances found in opium (morphine, codeine etc.). Opioid action is mediated by the receptors for endogenous opioids; peptides such as the enkephalins, the endorphins or the dynorphins. Opioids possess powerful analgesic and sedative effects, and are widely used as pain-killers. Their main side-effect is the rapid establishment of a strong addiction. Opioids receptors are G-protein coupled receptors (GPCR). There are four classes of receptors: mu (MOR), kappa (KOR) and delta (DOR), and the nociceptin receptor (NOP).

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- Gabrilovac, J., Balog, T., Martin-Kleiner, I. (2006). Signal transduction induced by opioids in immune cells: a review. *Neuroimmunomodulation*, 13, 1-7. ↗
- Pasternak, GW., Standifer, KM. (1997). G proteins and opioid receptor-mediated signalling. *Cell Signal*, 9, 237-48. ↗
- Hamm, HE. (1998). The many faces of G protein signaling. *J Biol Chem*, 273, 669-72. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2024-03-06	Edited	Schmidt, EE.

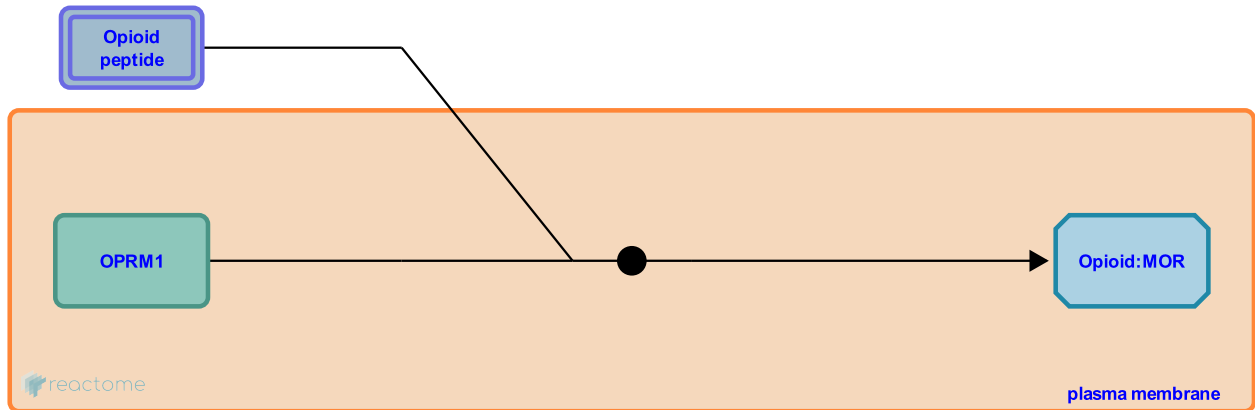
Opioid binds MOR ↗

Location: [Opioid Signalling](#)

Stable identifier: R-HSA-112042

Type: binding

Compartments: plasma membrane, extracellular region



The binding of an opiate peptide to the mu opiate receptor stabilises the receptor conformation in a state of high affinity, both for the ligand itself, and for the G-protein.

Preceded by: [Opioid dissociates from MOR](#)

Literature references

Wang, JB., Hawkins, AL., Persico, AM., Uhl, GR., Johnson, PS., Griffin, CA. (1994). Human mu opiate receptor. cDNA and genomic clones, pharmacologic characterization and chromosomal assignment. *FEBS Lett*, 338, 217-22. ↗

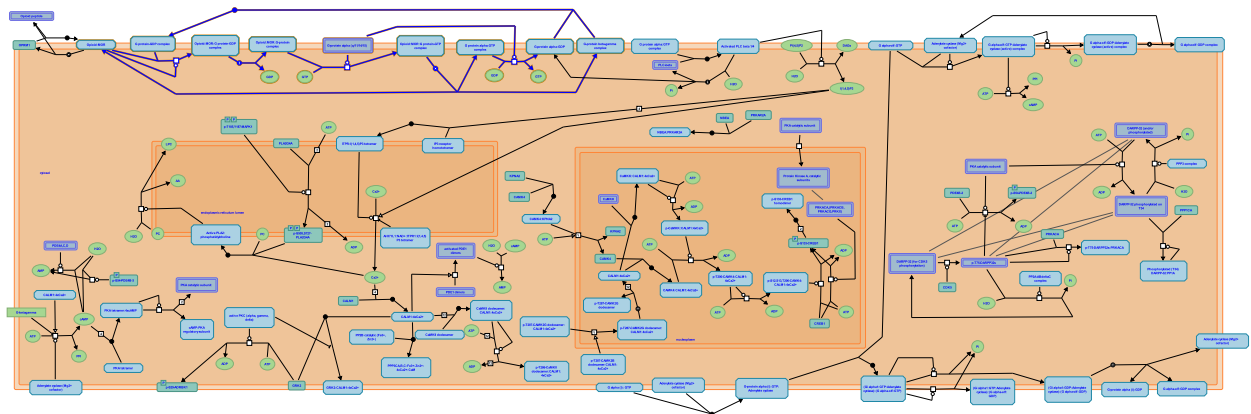
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G-protein activation ↗

Location: Opioid Signalling

Stable identifier: R-HSA-202040



 reactome

Receptor activated heterotrimeric G proteins consist of the Galpha and the tightly associated Gbeta-gamma subunits. When a ligand binds to a G protein-coupled receptor, it stabilises a conformation with an high affinity for the G-protein bound to GDP. GDP is then exchanged for GTP on the Galpha subunit. This exchange triggers the dissociation of the Galpha subunit from the Gbeta-gamma dimer and the receptor. Galpha-GTP and Gbeta-gamma, can then modulate different signalling cascades and effector proteins, while the receptor is able to activate another G protein, resulting in an amplification cascade. The Galpha subunit will eventually hydrolyze the attached GTP to GDP by its inherent enzymatic activity, allowing it to reassociate with Gbeta-gamma and start a new cycle.

Literature references

- Pasternak, GW., Standifer, KM. (1997). G proteins and opioid receptor-mediated signalling. *Cell Signal*, 9, 237-48. ↗
- Sora, I., Suzuki, T., Mizoguchi, H., Narita, M., Tseng, LF. (2002). Differential mechanism of G-protein activation induced by endogenous mu-opioid peptides, endomorphin and beta-endorphin. *Jpn J Pharmacol*, 89, 229-34. ↗
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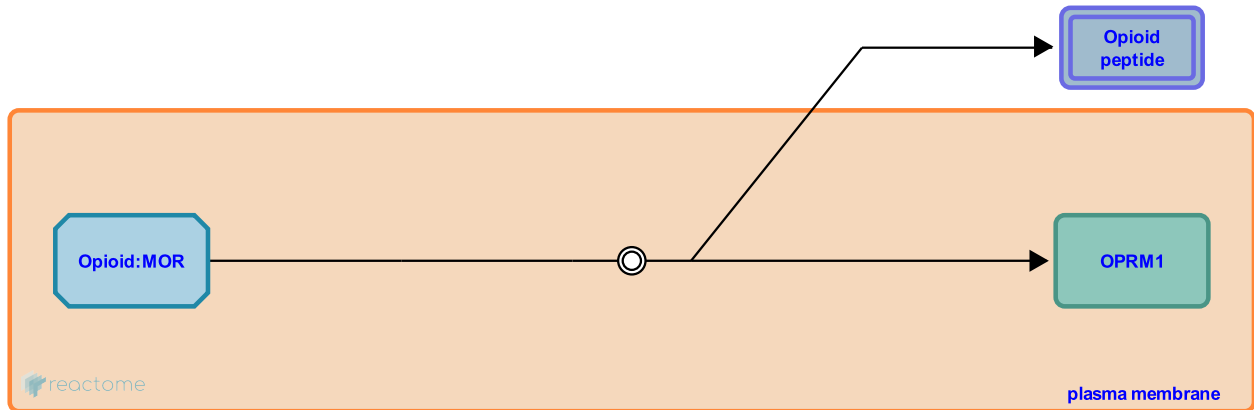
Opioid dissociates from MOR ↗

Location: [Opioid Signalling](#)

Stable identifier: R-HSA-167427

Type: dissociation

Compartments: plasma membrane, extracellular region



Different ligands of the MOR receptor can promote MOR phosphorylation, uncoupling, endocytosis or inactivation. For example, the endogenous peptide ligands at the MOR induce rapid desensitization, endocytosis and rapid receptor recycling. By contrast, morphine induces little to no endocytosis, tolerance and dependence. The agonist-dependent phosphorylation of opioid receptors changes the receptor conformation and increases the affinity of the receptors for cytosolic beta-arrestin proteins. This results in an uncoupling of G protein signalling and recruitment of the endocytotic machinery leading to receptor internalization and rapid resensitization. By contrast, PKC phosphorylation by non internalizing opioid ligands (e.g., morphine) cause receptors to remain inactivated in the plasma membrane, leading to signaling desensitization and opioid tolerance. In this case receptors appear to require activity of a phosphatase to be resensitized.

Followed by: [Opioid binds MOR](#)

Literature references

- Höllt, V., Mayer, D., Koch, T., Pfeiffer, M., Schulz, S., Stumm, R. (2004). Morphine induces terminal micro-opioid receptor desensitization by sustained phosphorylation of serine-375. *EMBO J*, 23, 3282-9. ↗
- Mundell, SJ., Oldfield, S., Hall, KJ., Braksator, E., Kelly, E., Henderson, G. et al. (2006). Agonist-selective mechanisms of mu-opioid receptor desensitization in human embryonic kidney 293 cells. *Mol Pharmacol*, 70, 676-85. ↗

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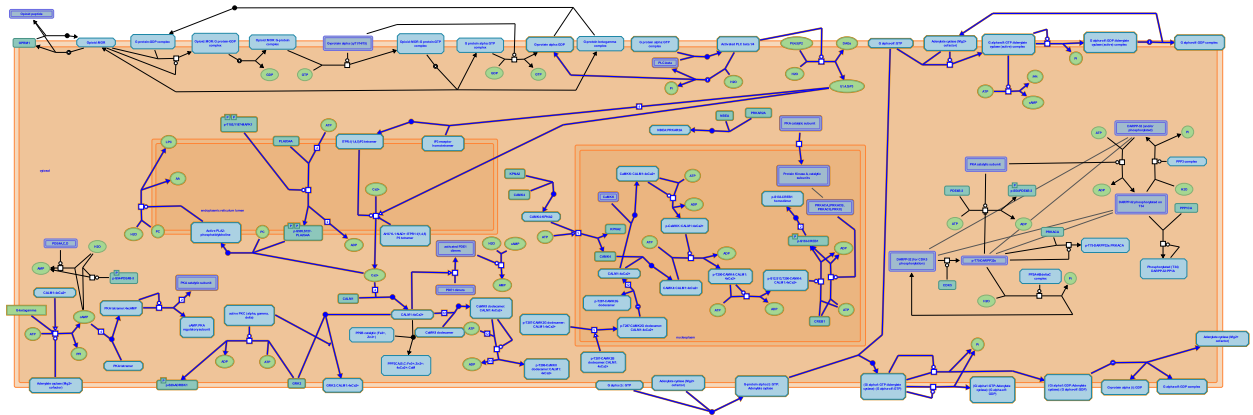
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G-protein mediated events ↗

Location: [Opioid Signalling](#)

Stable identifier: R-HSA-112040

Compartments: endoplasmic reticulum membrane, nucleoplasm, plasma membrane, endoplasmic reticulum lumen, cytosol



reactome

When dissociated G α -GTP and G β - γ can activate or inhibit different signalling cascades and effector proteins. The precise pathways depends on the identity of the alpha and beta/gamma subtypes.

Literature references

Pasternak, GW., Standifer, KM. (1997). G proteins and opioid receptor-mediated signalling. *Cell Signal*, 9, 237-48. ↗

Hamm, HE. (1998). The many faces of G protein signaling. *J Biol Chem*, 273, 669-72. ↗

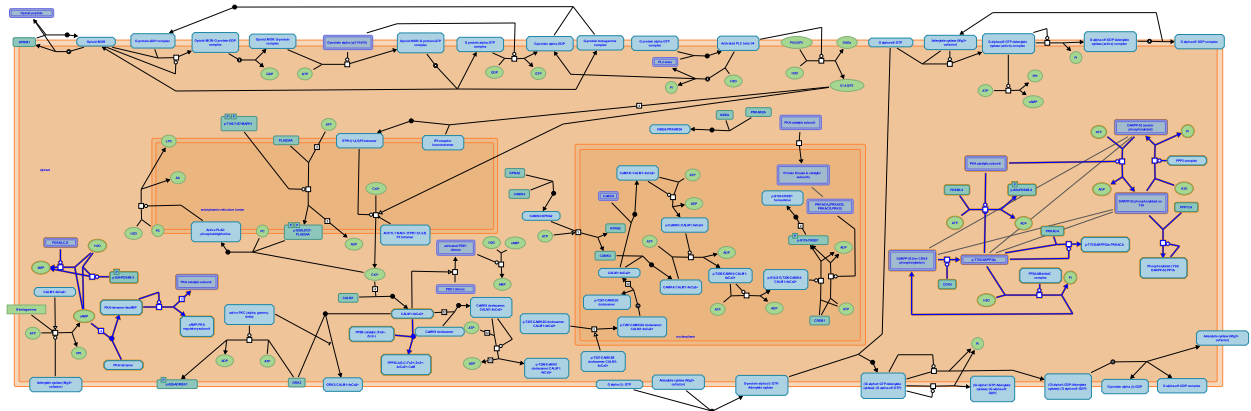
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DARPP-32 events ↗

Location: Opioid Signalling

Stable identifier: R-HSA-180024



reactome

Dopamine- and cAMP-regulated phosphoprotein, Mr 32 kDa (DARPP-32), was identified as a major target for dopamine and protein kinase A (PKA) in striatum. Recent advances now indicate that regulation DARPP-32 phosphorylation provides a mechanism for integrating information arriving at dopaminergic neurons, in multiple brain regions, via a variety of neurotransmitters, neuromodulators, neuropeptides, and steroid hormones. Activation of PKA or PKG stimulates DARPP-32 phosphorylation at Thr34, converting DARPP-32 into a potent inhibitor of protein phosphatase-1 (PP-1). DARPP-32 is also phosphorylated at Thr75 by Cdk5, converting DARPP-32 into an inhibitor of PKA. Thus, DARPP-32 has the unique property of being a dual-function protein, acting either as an inhibitor of PP-1 or of PKA.

Literature references

Svenningsson, P., Girault, JA., Fisone, G., Greengard, P., Nairn, AC., Nishi, A. (2004). DARPP-32: an integrator of neurotransmission. *Annu Rev Pharmacol Toxicol*, 44, 269-96. ↗

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Table of Contents

Introduction	1
❖ Opioid Signalling	2
↳ Opioid binds MOR	3
❖ G-protein activation	4
↳ Opioid dissociates from MOR	5
❖ G-protein mediated events	6
❖ DARPP-32 events	7
Table of Contents	8