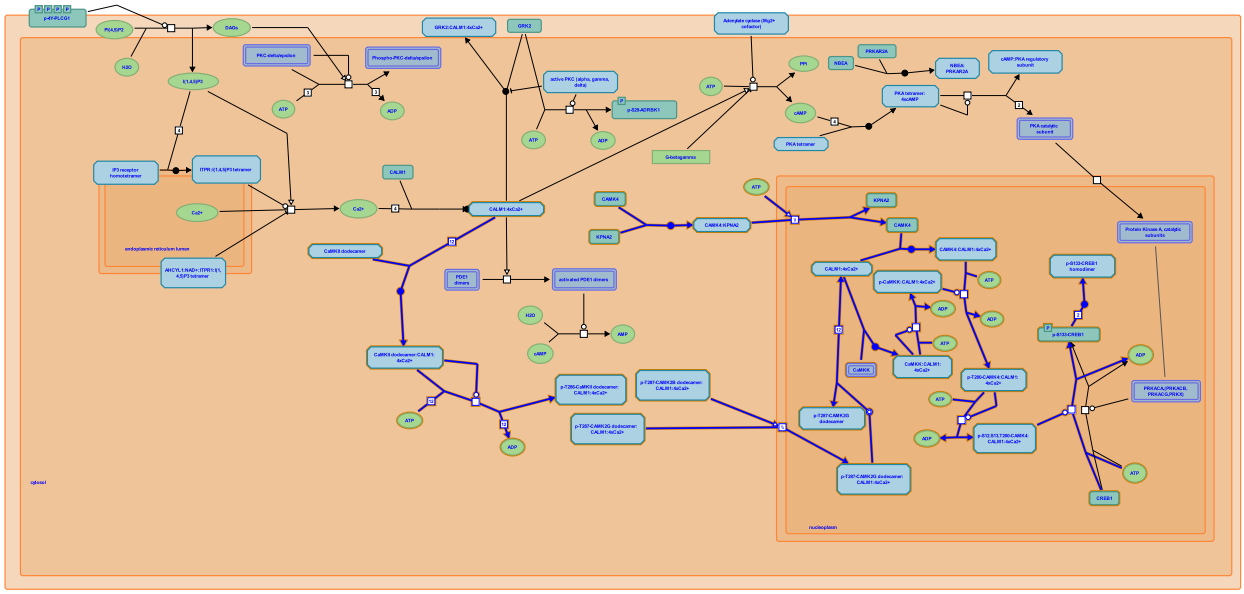
CaMK IV-mediated phosphorylation of CREB



Castagnoli, L., Gillespie, ME., Hansen, KB., Jassal, B., Le Novere, N., Lezza, AM., Mahajan, SS., Orlic-Milacic, M., Tukey, D., Yi, F.

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

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.

03/05/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

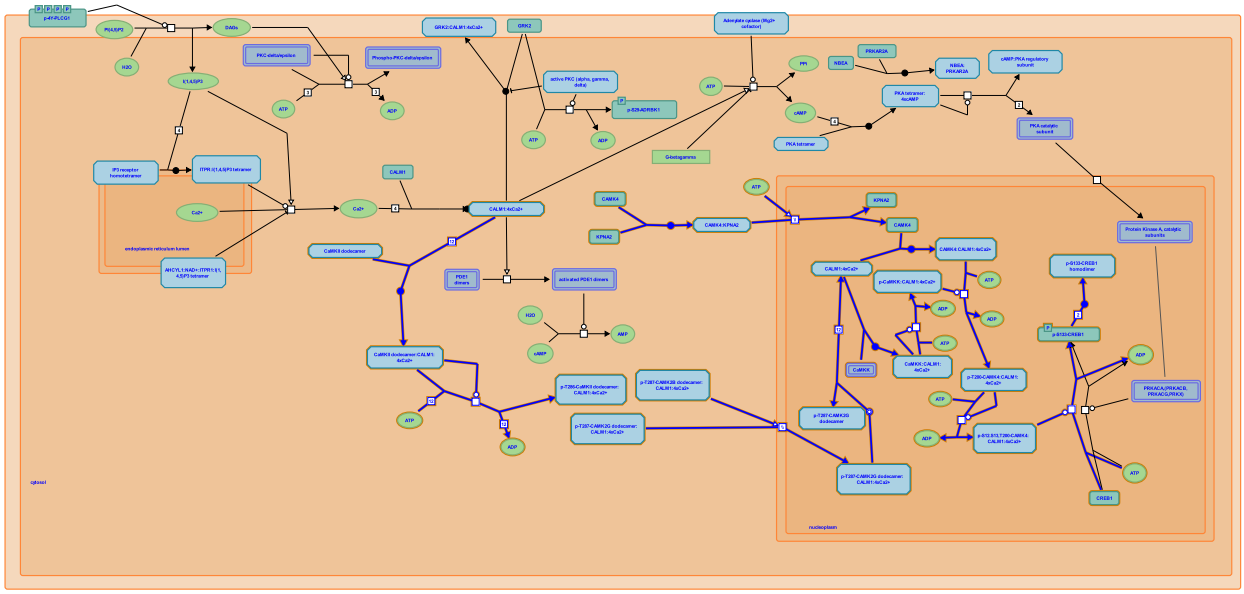
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

CaMK IV-mediated phosphorylation of CREB ↗

Stable identifier: R-HSA-111932

Compartments: nucleoplasm, cytosol



The Ca2+-calmodulin-dependent protein kinase (CaM kinase) cascade includes three kinases: CaM-kinase kinase (CaMKK); and the CaM kinases CaMKI and CaMKIV, which are phosphorylated and activated by CaMKK. Members of this cascade respond to elevation of intracellular Ca2+ levels. CaMKK and CaMKIV localize both to the nucleus and to the cytoplasm, whereas CaMKI is only cytosolic. Nuclear CaMKIV regulates transcription through phosphorylation of several transcription factors, including CREB. In the cytoplasm, there is extensive cross-talk between CaMKK, CaMKIV and other signaling cascades, including those that involve the cAMP-dependent kinase (PKA), MAP kinases and protein kinase B (PKB/Akt).

Literature references

Soderling, TR. (1999). The Ca-calmodulin-dependent protein kinase cascade. *Trends Biochem Sci, 24*, 232-6. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2018-10-10	Revised	Orlic-Milacic, M.

CaMKII binds activated calmodulin ↗

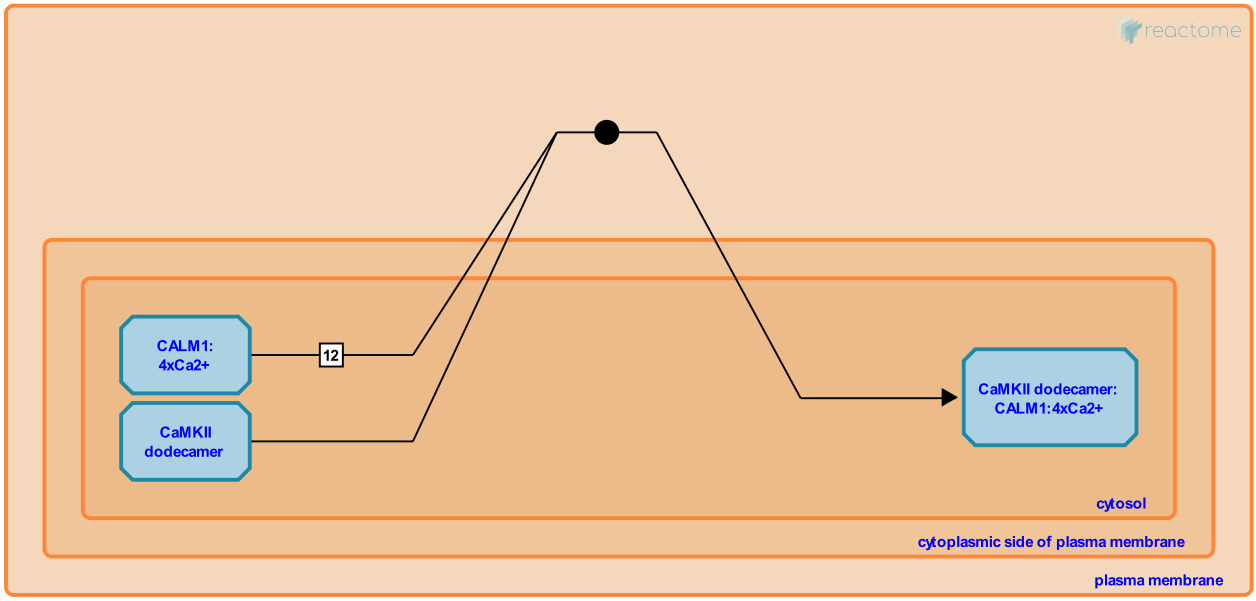
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-442725

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: CaMKII binds activated calmodulin (Rattus norvegicus)



CaMKII is fully activated upon binding to the complex of calcium and calmodulin (CALM1:4xCa2+), which forms upon influx of calcium ions through activated NMDA receptors. Autophosphorylation increases the affinity of CaMKII for the active calmodulin (CALM1:4xCa2+) (Meyer et al. 1992).

Followed by: CaMKII autophosphorylates

Editions

2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

CaMKII autophosphorylates ↗

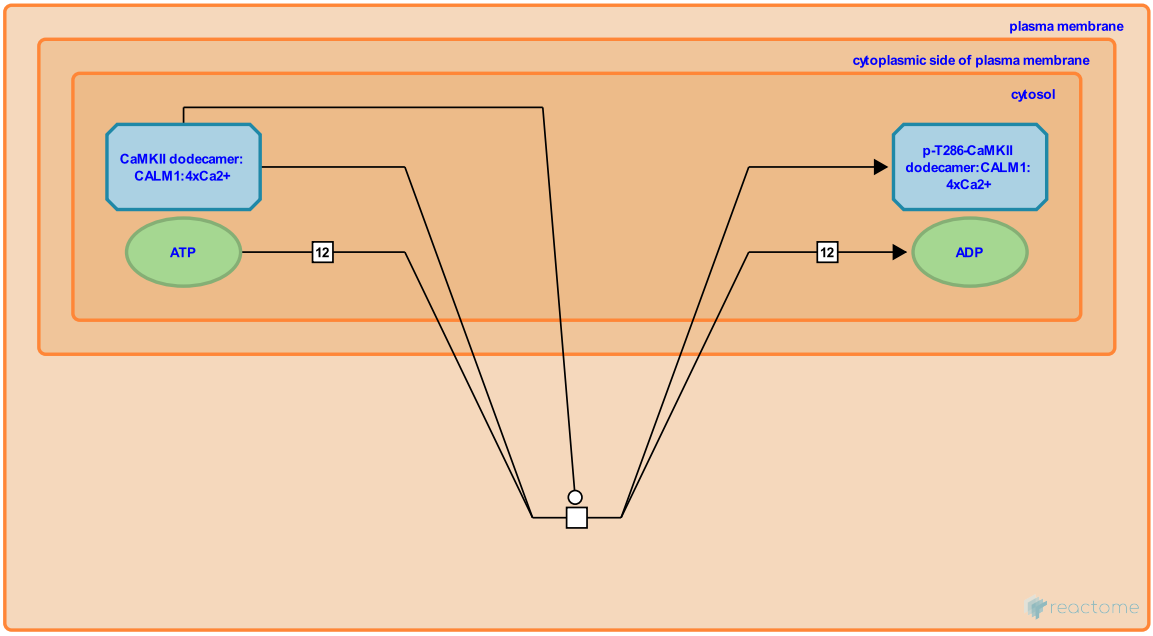
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-9617583

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: CaMKII autophosphorylates (Rattus norvegicus)



Binding of the complex of calcium and calmodulin (CALM1:4xCa2+) to CaMKII dodecamer, upon calcium influx through activated NMDA receptors, activates the kinase activity of CaMKII, leading to CaMKII autophosphorylation on threonine residue T286 (T286 in the alpha isoform of CaMKII corresponds to T287 in the beta isoforms of CaMKII). Autophosphorylation increases the affinity of CaMKII for calmodulin, but once autophosphorylated, CaMKII remains partially catalytically active even after dissociation of calmodulin (Schworer et al. 1986, Meyer et al. 1992).

Preceded by: CaMKII binds activated calmodulin

Followed by: Calmodulin-bound CaMKII-gamma enters the nucleus

Editions

2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

CAMK4 binds KPNA2 ↗

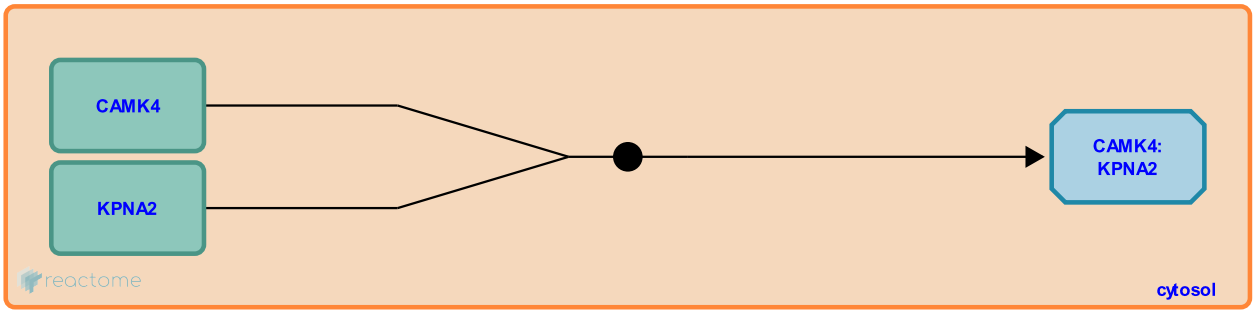
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-9619127

Type: binding

Compartments: cytosol

Inferred from: Camk4 binds Kpna2 (Mus musculus)



CAMK4 (CaMKIV) forms a complex with KPNA2 (Importin alpha-1). Importin beta is not required for the formation of this complex, but interferes with CAMK4 binding to KPNA2 (Kotera et al. 2005).

Followed by: CAMK4 enters the nucleus

Editions

2018-10-10	Authored	Orlic-Milacic, M.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

CAMK4 enters the nucleus ↗

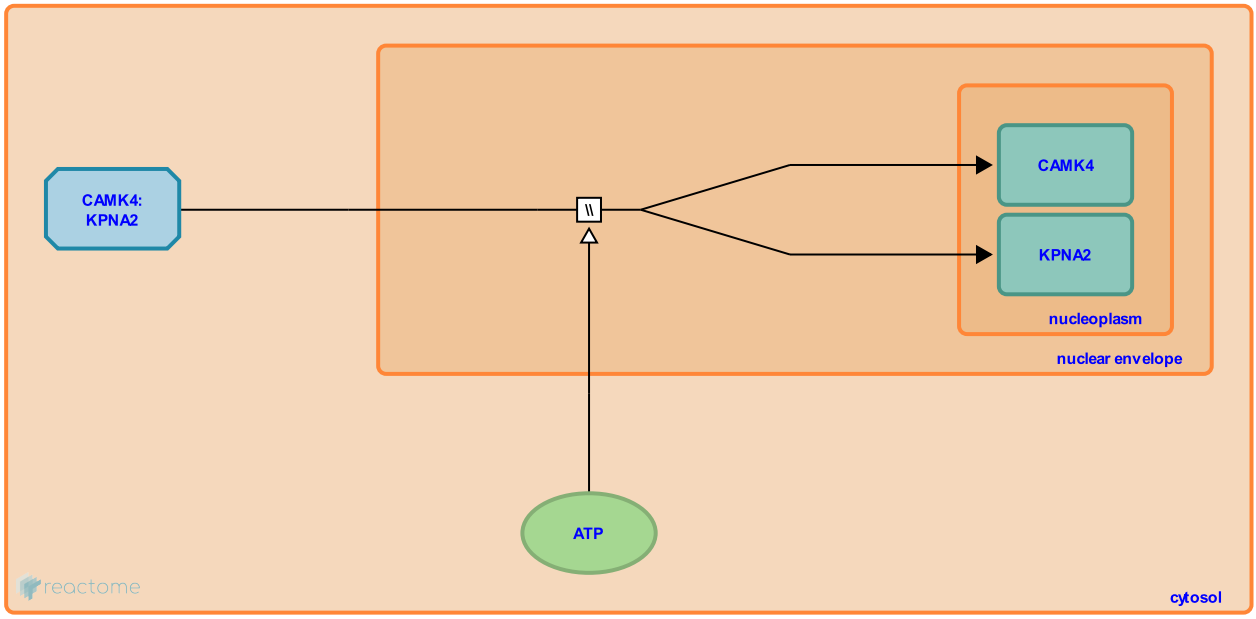
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-112282

Type: omitted

Compartments: nuclear envelope

Inferred from: Camk4 enters the nucleus (Mus musculus)



CAMK4 (CaMKIV) entry into the nucleus is facilitated by importin alpha (KPNA2). Importin beta and RAN GTPase are not needed for CAMK4 nuclear import (Kotera et al. 2004). CAMK4 nuclear import requires functional kinase domain of CAMK4 (Lemrow et al. 2004) and ATP, but ATP hydrolysis is not needed (Kotera et al. 2005).

Preceded by: CAMK4 binds KPNA2

Followed by: Calmodulin binds CAMK4

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

Calmodulin-bound CaMKII-gamma enters the nucleus ↗

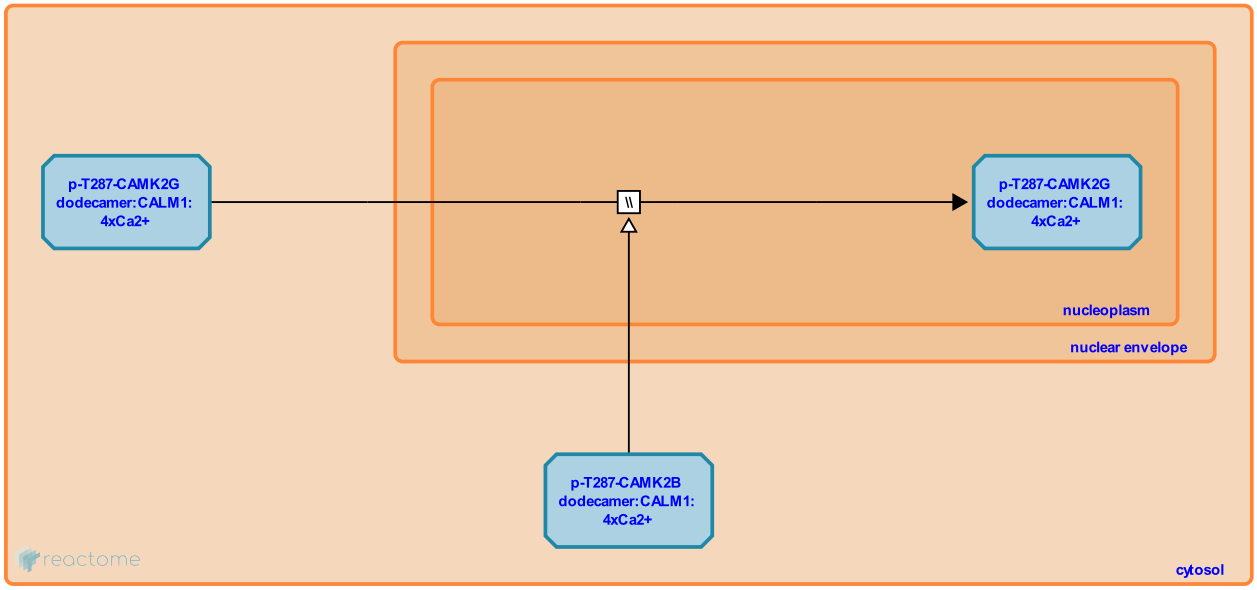
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-444792

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: CaM-bound CaMKII-gamma enters the nucleus (Rattus norvegicus)



Autophosphorylated, calmodulin-bound CaMKII-gamma (CAMK2G) translocates to the nucleus (Ma et al. 2014, Cohen et al. 2018). Translocation of CaMKII-gamma to the nucleus is positively regulated by activated CaMKII-beta through an unknown mechanism (Ma et al. 2014).

Preceded by: CaMKII autophosphorylates

Followed by: Activated calmodulin dissociates from CaMKII-gamma

Editions

2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2018-09-21	Revised	Orlic-Milacic, M.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

Activated calmodulin dissociates from CaMKII-gamma ↗

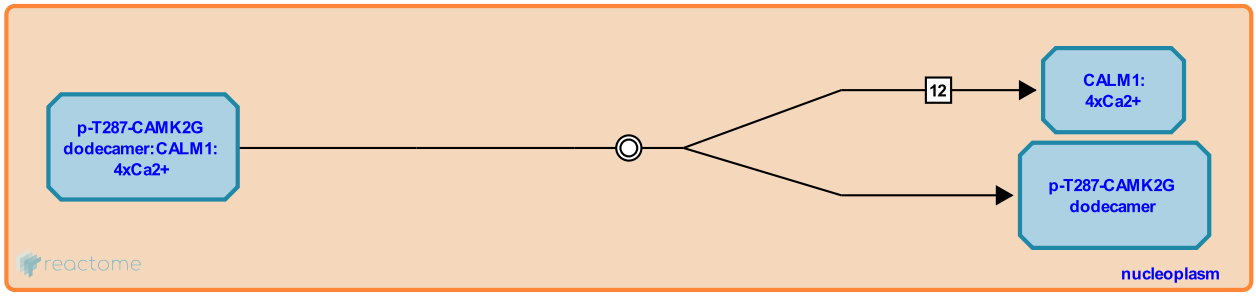
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-9618834

Type: dissociation

Compartments: nucleoplasm

Inferred from: Activated calmodulin dissociates from CaMKII gamma (Rattus norvegicus)



In the nucleus, activated calmodulin (CALM1:4xCa2+) dissociates from CaMKII-gamma (p-T287-CAMK2G dodecamer) (Ma et al. 2014, Cohen et al. 2018).

Preceded by: Calmodulin-bound CaMKII-gamma enters the nucleus

Followed by: Calmodulin binds CAMK4

Editions

2018-10-10	Authored	Orlic-Milacic, M.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

Calmodulin binds CAMK4 ↗

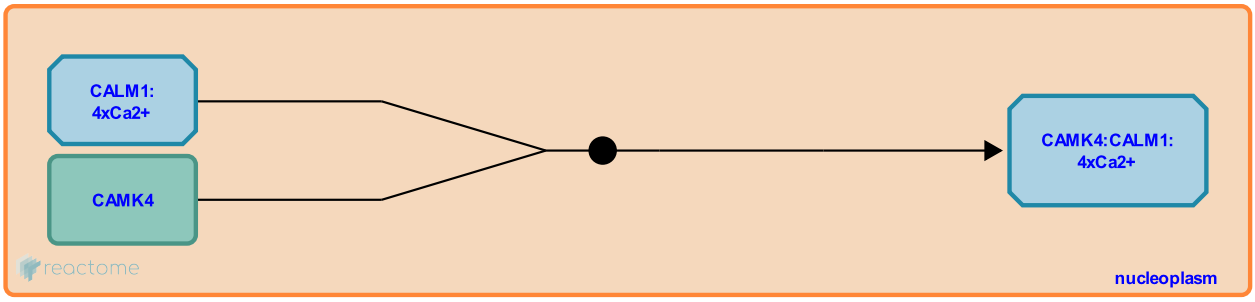
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-111913

Type: binding

Compartments: nucleoplasm

Inferred from: Calmodulin binds CaMK IV (Rattus norvegicus)



CaMKIV (CAMK4) becomes fully activated after a three-step mechanism. In the first step, upon a transient increase in intracellular calcium, calcium-bound calmodulin (Ca2+/CaM) binds to its autoregulatory domain, which relieves intersteric inhibition (Chatila et al. 1996, Tokumitsu et al. 2004). In the second step, an activating protein kinase, calcium/calmodulin-dependent protein kinase kinase (CaMKK), binds to the Ca2+/CaM:CaMKIV complex and phosphorylates CaMKIV on a threonine residue in the activation loop (Chatila et al. 1996, Anderson et al. 1998, Tokumitsu et al. 2004). In the third step, CaMKK-phosphorylated CAMK4 autophosphorylates on two serine residues at the N-terminus (Chatila et al. 1996). After full activation by the three-step mechanism mentioned above, the activity of CaMKIV becomes autonomous and no longer requires bound Ca2+/CaM. This activity is required for CaMKIV-mediated transcriptional regulation. The CaMKIV-associated PP2A then dephosphorylates CaMKIV, thereby terminating autonomous activity and CaMKIV-mediated gene transcription.

Preceded by: CAMK4 enters the nucleus, Activated calmodulin dissociates from CaMKII-gamma

Followed by: CaMKK phosphorylates CAMK4

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

CaMKK binds activated calmodulin in the nucleus ↗

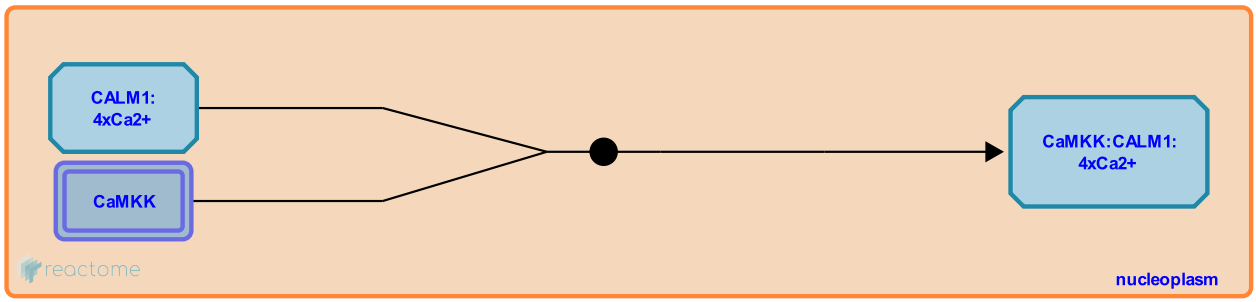
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-9618863

Type: binding

Compartments: nucleoplasm

Inferred from: Camkk1 binds activated calmodulin in the nucleus (Homo sapiens), CAMKK2 binds activated calmodulin in the nucleus (Homo sapiens)



Two isoforms of CaMKK, CAMKK1 (CaMKK alpha) and CAMKK2 (CaMKK beta) are expressed in the brain and involved in signaling downstream of the NMDA receptor (Schmitt et al. 2005, Mairet-Coello et al. 2013). CAMKK1 (Lee et al. 2010) and CAMKK2 (Kylarova et al. 2018) become catalytically active upon binding to the calcium-bound calmodulin (CALM1:4xCa2+). Calcium-bound calmodulin needs to translocate to the nucleus for CaMKK activation that precedes CAMK4 phosphorylation in glutamatergic neurons (Ma et al. 2014).

Followed by: CaMKK autophosphorylates in the nucleus

Editions

2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

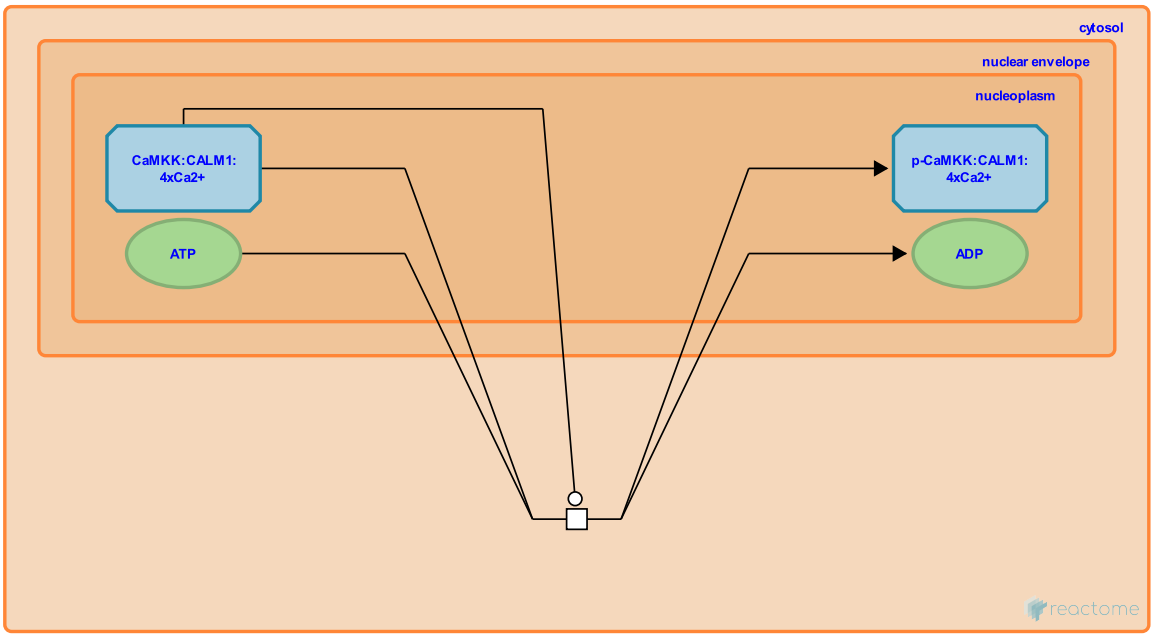
CaMKK autophosphorylates in the nucleus ↗

Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-442749

Type: transition

Compartments: cytosol



Both isoforms of CaMKK, CAMKK1 (CaMKK-alpha) and CAMKK2 (CaMKK-beta) are fully activated upon autophosphorylation, which, under physiological conditions, takes places after binding to the Ca2+/calmodulin complex (CALM1:4xCa2+) (Okuno et al. 1997, Yamamori et al. 2004). While several autophosphorylation sites in both CAMKK1 and CAMKK2 have been reported, it is not clear whether these sites are calmodulin-dependent and physiologically relevant (Tokumitsu et al. 2011, Scott et al. 2015). CAMKK1 is negatively regulated by phosphorylation of S74 and T108 by PKA. Constitutive phosphorylation of CAMKK2 by GSK3B and CDK5 may be required to prevent calmodulin-independent phosphorylation (Green et al. 2011). Once activated, CaMKK phosphorylates CaMKIV in a Ca2+/Calmodulin dependent manner (Yamamori et al. 2004). Because of uncertain localization of CaMKKs (Nakamura et al. 1996, Sakagami et al. 2000, Nakamura et al. 2001, Kitani et al. 2003), CaMKK autophosphorylation may occur in the nucleus, or in the cytosol, or in both cellular compartments.

Preceded by: CaMKK binds activated calmodulin in the nucleus

Followed by: CaMKK phosphorylates CAMK4

Literature references

Asai, M., Itoi, K., Takano, K., Yamamori, E., Yoshida, M., Oiso, Y. et al. (2004). Calcium/calmodulin kinase IV pathway is involved in the transcriptional regulation of the corticotropin-releasing hormone gene promoter in neuronal cells. *J Mol Endocrinol, 33*, 639-49. ↗

Editions

2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

CaMKK phosphorylates CAMK4 ↗

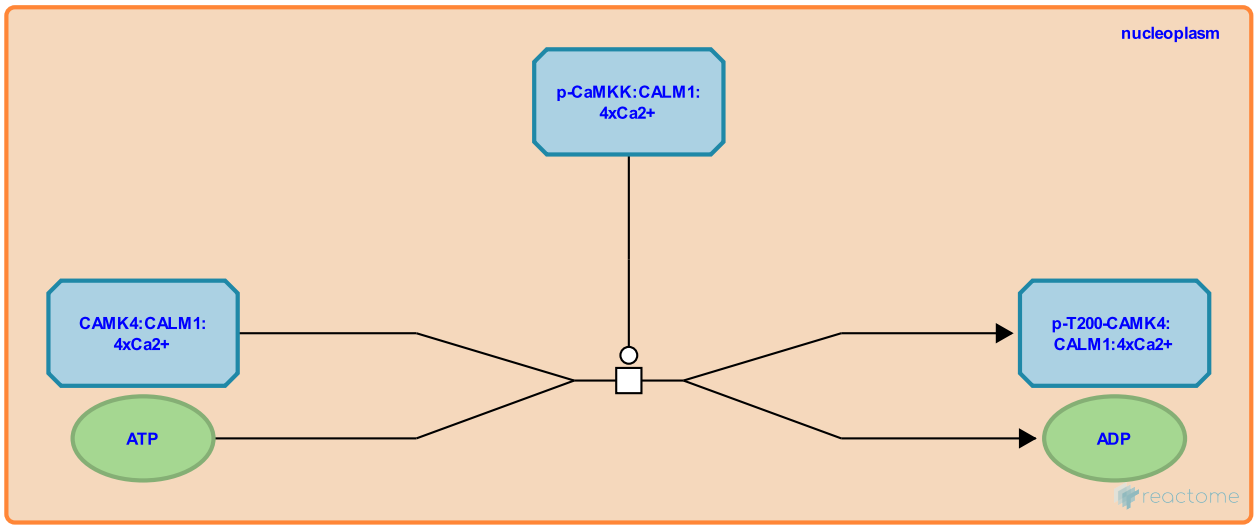
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-9619125

Type: transition

Compartments: nucleoplasm

Inferred from: Camkk2 phosphorylates CAMK4 (Homo sapiens), Camkk1 phosphorylates Camk4 (Rattus norvegicus)



Activated CaMKKs, CAMKK1 (CaMKK-alpha) and CAMKK2 (CaMKK-beta), phosphorylate calmodulin-bound CAMK4 (CaMKIV) on evolutionarily conserved threonine residue T200 (Chatila et al. 1996, Anderson et al. 1998, Tokumitsu et al. 2004).

Preceded by: CaMKK autophosphorylates in the nucleus, Calmodulin binds CAMK4

Followed by: CAMK4 autophosphorylates

Editions

2018-10-10	Authored	Orlic-Milacic, M.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

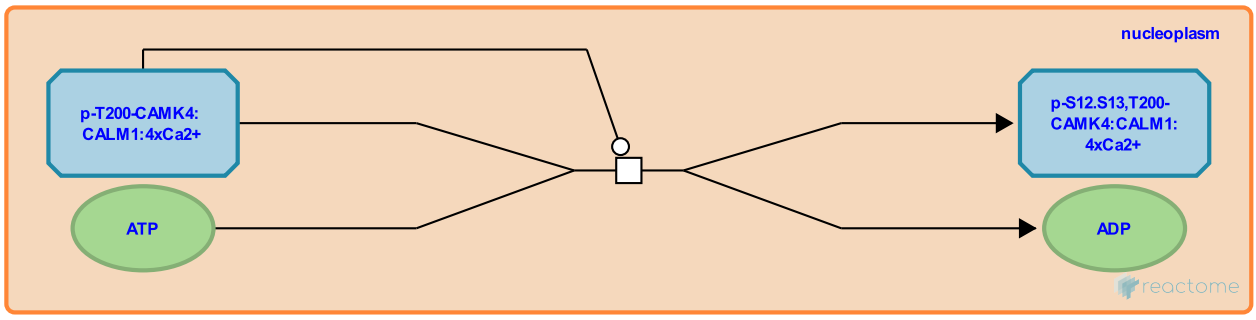
CAMK4 autophosphorylates ↗

Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-111915

Type: transition

Compartments: nucleoplasm



Autophosphorylation of the N-terminal serine residues, S12 and S13, of CAMK4 is required for full activation after Ca2+/calmodulin binding and phosphorylation of the Ca2+/calmodulin-bound enzyme on threonine residue T200 by a Ca2+/calmodulin-dependent protein kinase kinase (CAMKK1 or CAMKK2) (Chatila et al. 1996).

Preceded by: CaMKK phosphorylates CAMK4

Followed by: CaMK4 phosphorylates CREB1

Literature references

Ho, N., Anderson, KA., Means, AR., Chatila, T. (1996). A unique phosphorylation-dependent mechanism for the activation of Ca2+/calmodulin-dependent protein kinase type IV/GR. *J Biol Chem, 271*, 21542-8. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

CaMK4 phosphorylates CREB1 ↗

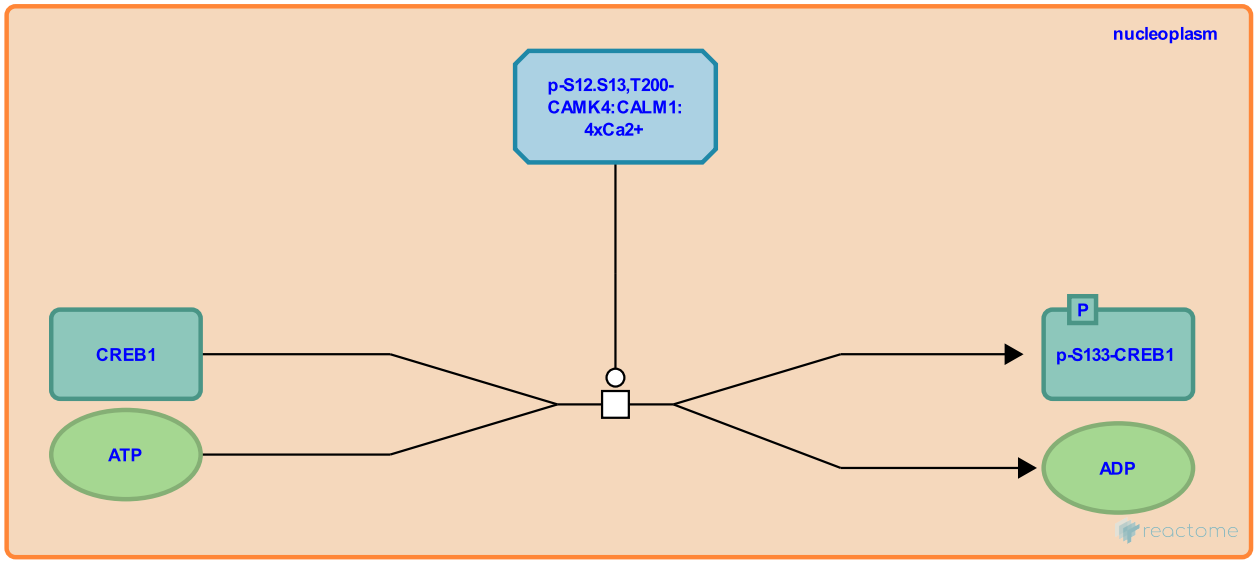
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-111912

Type: transition

Compartments: nucleoplasm

Inferred from: CaMKIV phosphorylates Creb1 (Rattus norvegicus)



The cAMP-responsive element binding protein (CREB), a key regulator of gene expression, is activated by phosphorylation on Ser-133. Several different protein kinases possess the capability of driving this phosphorylation, making it a point of convergence for multiple intracellular signaling cascades. Work in neurons has indicated that physiologic synaptic stimulation recruits a fast calmodulin kinase IV (CaMKIV)-dependent pathway that dominates early signaling to CREB. Activated CaMKIV (CAMK4) phosphorylates CREB1 at S133, thereby initiating the transcription of CREB1-regulated set of genes, leading to protein synthesis and long lasting changes that underlie synaptic plasticity.

Preceded by: CAMK4 autophosphorylates

Followed by: Dimerization of p-S133-CREB1

Literature references

Schumann, G., Klugmann, M., Guindalini, C., de Fonseca, FR., Perreau-Lenz, S., Schütz, G. et al. (2008). Loss of the Ca2+/calmodulin-dependent protein kinase type IV in dopaminoceptive neurons enhances behavioral effects of cocaine. *Proc Natl Acad Sci U S A, 105*, 17549-54. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2013-12-07	Reviewed	Lezza, AM.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

Dimerization of p-S133-CREB1 ↗

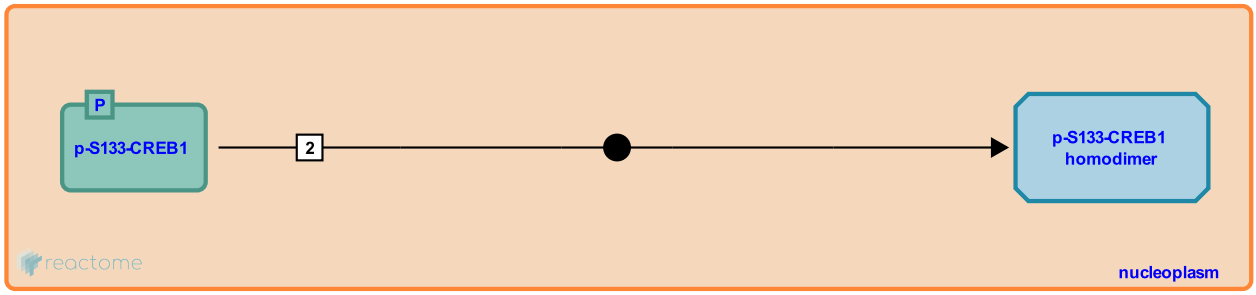
Location: CaMK IV-mediated phosphorylation of CREB

Stable identifier: R-HSA-111916

Type: binding

Compartments: nucleoplasm

Inferred from: Dimerization of p-S133-Creb1 (Rattus norvegicus)



Based on studies in rat cells, activation of CREB1 by phosphorylation at serine residue S133 induces formation of CREB1 homodimers which are able to bind DNA (Yamamoto et al. 1988). The DNA binding and dimerization domains reside in the C-terminal region of CREB1 (Yun et al. 1990).

Preceded by: CaMK4 phosphorylates CREB1

Editions

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

Table of Contents