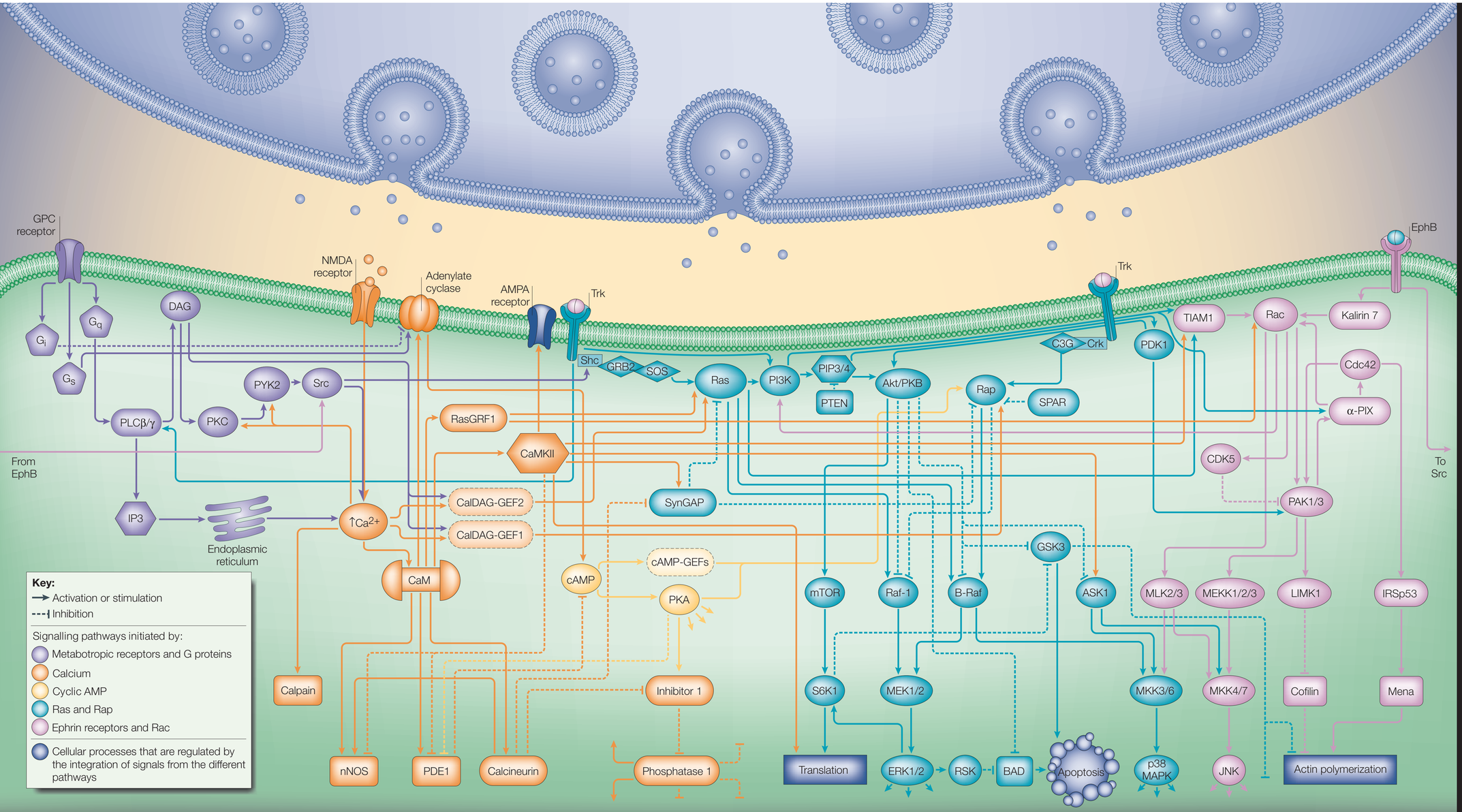
nature REVIEWS NEUROSCIENCE

Integrated biochemical signalling in postsynaptic spines

Mary B. Kennedy, Holly C. Beale, Holly J. Carlisle and Lorraine R. Washburn

Adjustments in the strength of excitatory synapses in neural networks are important for memory storage and maintenance of homeostasis in the brain. One important form of synaptic adjustment is 'spike-timing-dependent synaptic plasticity'. When presynaptic transmitter release occurs repeatedly a few milliseconds before action potentials in the postsynaptic neuron, long-term potentiation (LTP) of the synapse is induced; when release occurs repeatedly a few milliseconds after action potentials in the postsynaptic neuron, long-term depression (LTD) of the synapse is induced. This precise timing controls activation of the NMDA (*N*-methyl-D-aspartate)-type glutamate receptor, which allows influx of Ca^{2+} into the spine. Curiously, Ca^{2+} influx through the NMDA receptor is required to produce both LTP and LTD. Relatively rapid and large influxes of Ca^{2+} into the spine produce LTP, whereas more prolonged and lower influxes of Ca^{2+} produce LTD. Derangements in the pathways that regulate adjustments in synaptic strength can lead to excitotoxic neuronal death or to apoptosis, which underlie some neurodegenerative diseases. The poster summarizes studies on the signalling events that regulate postsynaptic function in and near the spine, and presents an initial attempt to understand how these pathways are organized to produce activity-dependent synaptic plasticity and homeostatic control.



The poster depicts pathways that control four postsynaptic physiological processes that are crucial for synaptic plasticity: regulation of AMPA-type glutamate receptors, polymerization of the actin cytoskeleton, local protein synthesis and gene expression. The first three are indicated in the diagram by blue symbols. Regulatory influences on gene expression are indicated by arrows and bars pointing towards the lower edge of the poster. The same pathways that control synaptic plasticity also regulate neuronal apoptosis (indicated by a blue symbol), which has an important role in brain development and contributes to the pathology of some neurodegenerative diseases. Five interlocking signalling pathways are depicted: those initiated by the second messengers Ca^{2+} (orange) and cyclic AMP (yellow); by growth factors and the small GTPases Ras and Rap (green); by ephrin receptors and the small GTPase Rac (pink); and by metabotropic receptors and G proteins (purple). Proteins depicted by symbols with lighter shading and a dashed outline are highly expressed in specific brain areas, but have not yet been explicitly implicated in postsynaptic regulation or directly localized to spines. Where possible, elements that reside near the plasma membrane are grouped near the top of the figure. Solid lines with arrows indicate activation or stimulation. Dashed lines with a bar indicate inhibition. We have not tried here to distinguish between small and large influences between proteins because their magnitudes will vary under different circumstances. The diagram is not meant to be exhaustive or definitive; rather, it is meant as a starting point for refining our understanding of the integration of signalling pathways in the spine.

Definitions: α-PIX, α-p21-activated kinase-interacting exchange factor; Akt, v-akt murine thymoma viral oncogene homologue; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ASK1 (MAP3K5), mitogen-activated protein kinase kinase kinase 5; BAD, BCL-associated death promoter; B-Raf, v-raf murine sarcoma viral oncogene homologue B1; C3G, Rap guanine nucleotide exchange factor (GEF) 1; CalDAG-GEF1/2, calcium and DAG-regulated guanine nucleotide exchange factor 1/2; CaM, calmodulin; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, cyclic AMP; Cdc42, cell division cycle 42; CDK5, cyclin-dependent kinase 5; Crk, v-crk sarcoma virus CT10 oncogene homologue (avian); DAG, diacylglycerol; EphB, ephrin B receptor; ERK1/2, extracellular signal-regulated kinase 1/2; GABA, γ-aminobutyric acid; GEF, guanine nucleotide exchange factor; G_i G_q, G_s, G proteins; GPC receptor, G-protein-coupled receptor; GRB2, growth factor receptor-bound protein 2; GSK3, glycogen synthase kinase 3; IP3, inositol 1,4,5-trisphosphate 3-kinase; IRSp53, brain-specific angiogenesis inhibitor 1-associated protein 2; JNK, c-Jun amino-terminal kinase; Kalirin 7, RhoGEF kinase; LIMK1, LIM-domain-containing protein kinase 1; MAPK, mitogen-activated protein kinase; MEK1/2, MAPK/ERK kinase1/2; MEKK1/2/3, mitogen-activated protein kinase kinase kinase 1/2/3; Mena, mammalian enabled; MKK3/4/6/7, mitogen-activated protein kinase kinase 3/4/6/7; MLK2/3, mitogen-activated protein kinase kinase kinase 10/11; mTOR, mammalian target of rapamycin; NMDA, *N*-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; p38 MAPK, p38 mitogen-activated protein kinase; PAK1/3, p21-activated kinase 1/3; PDE1, phosphodiesterase 1; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphatidylinositol 3-kinase; PIP3/4, phosphatidylinositol-bisphosphate 3/4; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PLCβ/γ, phospholipase C-β/γ; PTEN, phosphatase and tensin homologue; PYK2, protein tyrosine kinase 2; Rac, Rap, Ras, small GTPases; Raf-1, v-raf-1 leukaemia viral oncogene 1; RasGRF1, Ras-guanine nucleotide-releasing factor 1; RSK, ribosomal protein S6 kinase; S6K1, S6 protein kinase 1; Shc, Src homology 2 domain-containing transforming protein C; SOS, son of sevenless; SPAR, spine-associated Rap GTPase-activating protein; Src, Src family of non-receptor tyrosine kinases; SynGAP, synaptic GTPase-activating protein; TIAM1,T-cell lymphoma invasion and metastasis 1; Trk, tyrosine receptor kinase.