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Molecular mechanisms underlying neuronal synaptic plasticity: systems biology meets computational neuroscience in the wilds of synaptic plasticity

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Abstract

Interactions among signaling pathways that are activated by transmembrane receptors produce complex networks and emergent dynamical behaviors that are implicated in synaptic plasticity. Temporal dynamics and spatial aspects are critical determinants of cell responses such as synaptic plasticity, though the mapping between spatio-temporal activity pattern and direction of synaptic plasticity is not completely understood. Computational modeling of neuronal signaling pathways has significantly contributed to understanding signaling pathways underlying synaptic plasticity. Spatial models of signaling pathways in hippocampal neurons have revealed mechanisms underlying the spatial distribution of ERK activation in hippocampal neurons. Other spatial models have demonstrated that the major role of anchoring proteins in striatal and hippocampal synaptic plasticity is to place molecules near their activators. Simulations of yet other models have revealed that the spatial distribution of synaptic plasticity may differ for potentiation versus depression. In general, the most significant advances have been made by interactive modeling and experiments; thus, an interdisciplinary approach should be applied to investigate critical issues in neuronal signaling pathways. These issues include identifying which transmembrane receptors are key for activating ERK in neurons, and the crucial targets of kinases which produce long lasting synaptic plasticity. Though the number of computer programs for computationally efficient simulation of large reaction-diffusion networks is increasing, parameter estimation and sensitivity analysis in these spatial model remains more difficult than in single compartment models. Advances in live cell imaging coupled with further software development will continue to accelerate the development of spatial models of synaptic plasticity.

INTRODUCTION

Long term synaptic plasticity is the long lasting change in synaptic strength produced by diverse stimulation protocols, both in vivo and in vitro. Changes in synaptic strength observed in vivo[1] or in vitro after learning[2], suggest that synaptic plasticity is one of the mechanisms that underlies long term memory storage[3]. Long term synaptic plasticity may be subdivided into long term depression (LTD), in which synaptic strength decreases, and long term potentiation (LTP), in which synaptic strength increases. In some experiments, two different sets of synapses are monitored while the induction protocol is applied to a single set of synapses[4]. In this situation, homo-synaptic plasticity refers to the change in synaptic strength being limited to those synapses receiving the induction protocol; in contrast, hetero-synaptic plasticity refers to a change in synaptic strength observed in the synapses not receiving the induction protocol. Stimulation protocols producing synaptic

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plasticity vary widely, and often protocols that produce potentiation in one brain region will produce no plasticity or even depression in another brain region.

Though the molecular mechanisms leading to synaptic plasticity are quite diverse, all synaptic plasticity requires an elevation in intracellular calcium in the post-synaptic neuron[4, 5]. In many cell types the source of calcium is influx through NMDA receptors in response to conjunction of depolarization and glutamate release. In other cell types the source of calcium is influx through voltage dependent calcium channels[6, 7], or release of calcium from intracellular stores[8]. Possibly the most important calcium binding protein with respect to synaptic plasticity is calmodulin [9], which then binds to calcium-calmodulin dependent protein kinase type 2 (CaMKII) to produce LTP [10] or protein phosphatase 2B (calcineurin)[11] to produce LTD. The prevailing hypothesis is that with a low calcium influx, calcium binds to calmodulin to activate calcineurin, which dephosphorylates various targets; when calcium influx is higher, CaMKII is activated and phosphorylates AMPA receptors[12]. Experimental studies[4, 5] as well as computational models[13–15] have demonstrated how hippocampal synaptic plasticity is controlled by the calcium elevation and subsequent activation of CaMKII or calcineurin.

Though calcium and downstream pathways are indeed required for synaptic plasticity, other signaling pathways are critical in certain forms of plasticity or in some brain regions. In the cerebellum and striatum, synaptic plasticity crucially requires activation of G protein coupled receptors[16–18], and some long lasting, protein synthesis dependent forms of hippocampal synaptic plasticity cannot be explained by CaMKII and calcineurin alone. For example, both striatal LTP[19] and long lasting hippocampal LTP induced using four spaced trains of 100 Hz[20] require protein kinase A (PKA) activation. Because these signaling pathways are important yet less familiar to computational neuroscientists, this review focuses on those forms of synaptic plasticity that additionally require signaling pathways other than calcium activation of CaMKII.

The organization of the manuscript is as follows. We first briefly review two classes of transmembrane receptors and G proteins which have been implicated in various forms of synaptic plasticity and have been extensively studied in systems biology. Then we describe some of the non-linear, spatial and temporal aspects of signaling pathways which necessitates computational modeling. Next we present some of the spatial, computational models which evaluate these non-linear interactions among signaling pathways underlying synaptic plasticity. Though synaptic plasticity is found in most brain regions and many cell types, only models describing plasticity of principal neurons of hippocampus, cerebellum and striatum are included. Lastly, we explain several crucial issues where future modeling could contribute to a deeper understanding of the synaptic plasticity underlying long term memory storage.

Signaling Pathway Initiation via Transmembrane Receptors

Signaling pathways are activated via transmembrane receptors such as the receptor tyrosine kinases (RTK) and the G protein coupled receptors (GPCRs). The importance of these receptors for disease is reflected in the large proportion of pharmaceuticals which target receptors[21]. Furthermore, synaptic plasticity in many brain regions requires activation of G protein coupled receptors, or receptor tyrosine kinase involvement[22]. Receptor tyrosine kinases bind neuropeptides such as brain derived neurotrophic factor (BDNF), causing dimerization, which activates the kinase activity. Subsequent phosphorylation of the receptor leads to recruitment of several scaffolding and adaptor proteins and ultimately activation of monomeric GTP binding proteins, also known as small GTPases. These GTPases typically bind to and activate a kinase in the mitogen-activated protein kinase (MAPK) cascade [23]. GPCRs typically bind amino acid or catecholamine neurotransmitters

and are coupled to heterotrimeric GTP binding proteins (G proteins) that associate with intracellular loops of the GPCR[24]. Binding of neurotransmitter triggers a conformational change which stabilizes dissociation of guanosine diphosphate from the α subunit of the G protein (Gα), followed by binding of guanosine triphosphate (GTP), and dissociation of GαGTP from the G protein βγ subunits (Gβγ)[25]. Both GαGTP and Gβγ can bind to various effectors, such as phospholipase C and adenylyl cyclase, which produce second messengers, such as diacylglycerol and cyclic adenosine monophosphate (cAMP), respectively, which ultimately activate kinases such as protein kinase C (PKC) and PKA, respectively. Consequent to both types of transmembrane receptors, not only kinases but also phosphatases and other inactivation mechanisms are initiated.

Interactions form Networks of Signaling Pathways

Signaling pathways initiated by these receptors are not simple linear pathways of molecules; rather they are complex networks of interacting pathways with convergence, divergence, and positive and negative feedback loops. The non-linear dynamics produced by these interactions have been extensively studied in systems biology[26]; the subset of examples provided here are selected based on their relevance in synaptic plasticity. Activation of the extracellular-signal related kinase (ERK1/2) forms of MAPK is an excellent example of convergence as ERK1/2 is activated through multiple pathways, initiated by both GPCRs and RTKs. In PC12 cells, the RTK that binds eurokaryotic growth factor activates ERK1/2 through the small GTPase Ras and the kinases c-Raf and B-Raf; whereas a different RTK, activates ERK1/2 via the small GTPase Rap1 and the kinase B-Raf (Fig 1A, C)[23, 27]. PKC, which is activated by several GPCRs, also can lead to ERK1/2 activation and is required for cerebellar synaptic plasticity[28, 29]. Divergence occurs at multiple stages subsequent to receptor activation (Fig 1B). Divergence in signaling is exhibited by cAMP which can activate cyclic nucleotide gated channels, PKA and the guanosine exchange factor activated by cAMP (EPAC)[30]. Divergence also occurs downstream of cAMP as PKA has numerous phosphorylation targets, such as glutamate receptors, β-adrenergic receptors, phosphodiesterases, etc. Feedback loops, both positive and negative, occur within pathways and also are formed by interactions between pathways. ERK1/2 is involved in a positive feedback loop (Fig 1C) with PKC and phospholipase A_2 (PLA_2), which is critical for LTD in the cerebellum[18, 28]. Consequently, disruption of either PKC or MAPK is sufficient to block cerebellar LTD[28]. An example of a negative feedback loop is found in the cAMP signaling pathway[31] (Fig 1D). PKA phosphorylation of some phosphodiesterase isoforms, such as type 4 and 10, enhances their ability to degrade cAMP; thus, PKA limits its own activity. This negative feedback loop is in operation in the hippocampus, and inhibition of type 4 phosphodiesterases, a major component of phosphodiesterase activity in hippocampal neurons, enhances hippocampal LTP[32, 33]. These motifs are only a subset of the types of interactions formed by complex networks of signaling pathways[34, 35] and implicated in synaptic plasticity.

Critical Contribution of Spatial Interactions and Temporal Dynamics

Activation of specific molecules may be less important than location and temporal dynamics of molecule activation. Spike timing dependent plasticity (STDP) is a striking temporal phenomenon in which precise timing of the post-synaptic action potential influences the direction of plasticity[36]. The induction of STDP requires repeated pairings of synaptic stimulation with a post-synaptic action potential. The direction of plasticity depends on whether the action potential precedes or follows the post-synaptic EPSP. Another example of temporal sensitivity is found in the hippocampus area CA1, in which four trains of 100 Hz produce a long lasting LTP which is PKA dependent when the trains are given 5 min apart, but PKA independent when given 3 sec apart[37]. A model of the calcium and cAMP activated signaling pathways explained the underlying mechanism[38] by demonstrating that

CaMKII and PKA have opposite temporal sensitivities; thus PKA activity is enhanced and CaMKII activity is reduced in response to four trains given 5 min apart. In addition to these examples in neurons, numerous experimental studies demonstrate that distinct biological responses are produced by different dynamics of MAPK activation[23, 39], suggesting that control by temporal dynamics is widespread.

The spatial aspect of cell signaling is even more important and has only recently begun to be understood. Given that environmental stimuli are converted into spatial patterns of synaptic input, pattern discrimination requires some degree of spatial specificity. If all synapses of a neuron were potentiated in response to synaptic stimulation, then the neuron would respond not only to previously learned patterns, but also any arbitrary pattern of synaptic input[40]. Indeed, theoretical analysis of information capacity in networks assumes that synaptic weights are independent[41]. Because activation of signaling pathways underlies synaptic plasticity, spatial specificity of synaptic plasticity requires spatial specificity of at least a subset of signaling pathway molecules. Hetero-synaptic metaplasticity [42], in which the threshold for plasticity at one set of spines modifies the subsequent LTP induction in a distinct but nearby set of spines, and the spatial specificity of two pathway experiments[4] confirm the ability of neurons to potentiate a subset of synapses in response to synaptic stimulation.

Spatial gradients of signaling molecules are prominent in neurons due to their elongated dendritic structures. Synaptic inputs in one part of the dendrite lead to second messenger production and diffusion to other parts of the dendrite. Inactivation mechanisms, such as phosphodiesterases for cAMP[31] or pumps and buffers for calcium[43], limit the diffusional distance of these second messengers (Fig 2A) and sharpen spatial gradients. Equally important are scaffolding or anchoring proteins that organize interacting molecules into multi-protein complexes. A-kinase anchoring proteins (AKAPs) are a family of proteins that anchor PKA together with a complement of other proteins such as β-adrenergic receptors, phosphodiesterases, adenylyl cyclase, PKC, and calcineurin[44]. AKAP12 and AKAP5 are both highly expressed in the hippocampus and striatum[45, 46], and AKAP12 in particular is critical for PKA dependent forms of hippocampal LTP[46]. PKA anchoring together with phosphodiesterase control of cAMP diffusion create microdomains of PKA activation and allow different neuromodulators to activate different PKA targets in neurons[47], as has been observed in cardiac myocytes[48]. The complexity of these signaling pathways coupled with diversity in dynamics and spatial compartmentalization makes it difficult to understand the function of single molecules or the integrated control of cell function[26].

COMPUTATIONAL MODELING OF NEURONAL SIGNALING PATHWAYS

Modeling has made significant contribution to understanding the complexity of signaling pathway interactions in neurons. In particular, models of signaling pathways have been developed to investigate spatial and temporal aspects of LTP and LTD, two phenomena thought to underlie memory storage. Several kinases and phosphatases are strongly implicated in synaptic plasticity, including the kinases ERK1/2, PKC, PKA and CaMKII and the phosphatases calcineurin, PP1 and PP2A, though the relative importance of each molecule depends on the brain region or cell type. Though there are many non-spatial models of signaling pathways,the next section focuses on models incorporating significant morphological features of neurons, such as a soma with an elongated dendrite, or a dendrite with spines.

Two interrelated questions are: which mechanisms underlie the all or none phosphorylation of ERK1/2 in a subset of dendrites in hippocampal area CA1 after induction of LTP and what produces a spatial gradient of ERK1/2 activation from those dendrites to the soma. The

first question was addressed with a series of models of ERK1/2 activation[49], and evaluated the ability of two general mechanisms to account for spread of ERK1/2 phosphorylation more than 100 μm along a dendrite: diffusion from a single point of calcium influx , or calcium influx at multiple points along the dendrite. Signaling pathways included the PKC-PLA_2-ERK1/2 positive feedback loop, and two additional feedforward activation pathways for ERK1/2: directly via calcium-calmodulin, and via activation of the protein kinase C isoform called PKMζ. Simulations, confirmed by experiments, showed that diffusion was not sufficient to explain the spatially-extended, phosphorylated ERK1/2, and that either distributed synaptic input or a dendritic action potential, which creates an extended area of calcium elevation, was required[49]. The strength of this modeling study was the systematic evaluation of several alternative mechanisms, and the close comparison with both electrophysiology and immunocytochemical data. In addition, the sensitivity of the results to diffusion constant and calcium influx were evaluated. The second question was addressed by investigating the control of microdomains of signaling pathways downstream of the β-adrenergic receptor in the soma and dendrite of a hippocampal pyramidal neuron[50]. The model included activation of adenylyl cyclase, production of cAMP, and activation of PKA, which led to activation of the ERK1/2 cascade. Phosphodiesterases inactivated the cAMP, and two phosphatases turned off several kinases in the model. Simulations revealed two main factors controlling the spatial gradients: dendritic diameter, and negative regulators such as phosphodiesterases and phosphatases. The strength of this publication was the thorough evaluation of diffusion constants and other kinetic rate constants on the main result, as well as close comparison to experimental data. Both of these models were implemented deterministically, i.e. using numerical approximation to the partial differential equations describing diffusion along concentration gradients. A weakness shared by both studies was the lack of dendritic spines in the models, and the minimal interaction between the biochemical model and electrical activity of a CA1 pyramidal neuron model. These weaknesses were addressed in a subsequent model[51] in which calcium influx from an electrical model directly activated the biochemical reactions, and conductance of two channels in the electrical model were controlled by the biochemical model: activated ERK modified the transient potassium channel and phosphorylation dependent AMPAR trafficking modified AMPAR conductance. Simulations of LTP induction in the presence of background synaptic input revealed a form of homeostatic synaptic plasticity: stimulated spines exhibited potentiation, but non-stimulated spines exhibited depression. All three of these models implemented different pathways for activation of ERK; yet, as discussed below, several other pathways also may be activating ERK in neurons. Another issue addressed with spatial models is the role of anchoring proteins in synaptic plasticity (Fig 2B). Experimental data showed that anchoring of PKA by AKAP is required for hippocampal LTP[52], but it did not reveal whether anchoring near the activating molecules, such as adenylyl cyclase, or target molecules, such as AMPA receptors, is more important. To address this question, a model of signaling pathways activated by calcium and GPCRs coupled to adenylyl cyclase was created in a CA1 pyramidal neuron dendrite with spines[53]. Because of the small numbers of molecules in the spine, the model was implemented using software for computationally efficient simulation of stochastic reaction-diffusion systems. The signaling pathways were activated using four trains of 100 Hz stimulation separated by 80 sec, a stimulation paradigm demonstrated to produce PKA dependent LTP[38]. PKA was colocalized either with its activator adenylyl cyclase, or its targets, such as AMPA receptors, or both. Simulations showed that PKA activity was higher when localized with adenylyl cyclase, due to strong inactivation mechanisms for cAMP. A strength of this model is the use of stochastic simulations required by the small numbers of molecules in dendritic spines. On the other hand, this model shares the weakness regarding the lack of interaction between the biochemical model and neuronal electrical activity. One weakness shared by all of these hippocampal models relates to the simulation time. None of the above models simulated beyond 50 minutes (and simulation time was usually far shorter), which is not sufficient to

assess mechanisms relevant for the long lasting LTP underlying memory. Continuing the simulation for longer is not sufficient since these models also do not include the protein synthesis pathways (as discussed below).

Two other brain regions: striatum and cerebellum, have been the subject of spatial models of signaling pathways activated by G protein coupled receptors. In the cerebellum, LTD requires coincident stimulation of glutamatergic parallel fibers and climbing fibers[18], which together produce a supralinear increase in calcium caused by release of calcium via the inositol triphosphate receptor channels on the endoplasmic reticulum. In the striatum, LTP requires activation of dopamine D1 receptors (D1R)[16, 17] which are coupled via G proteins to adenlylate cyclase[54]. On the other hand, LTD requires production of endocannabinoids[55] mediated by activation of receptors coupled to the Gαq subtype of G proteins, which bind to and activate phospholipase C[56]. Models of synaptic plasticity in these structures have investigated spatial specificity of synaptic plasticity at a higher resolution by addressing whether the elevation in signaling molecule concentration is restricted to stimulated spines.

To investigate spatial specificity in the striatum, a model of calcium and D1R coupled signaling pathways was created in a medium spiny neuron dendrite with multiple spines[57]. This model was implemented stochastically, with the PKA holoenzyme colocalized with the D1R/G protein/adenylyl cyclase complex. Simulations of the response to dopamine release at one end of the dendrite revealed that cAMP exhibits spatial gradients with a spatial decay constant of ~5 μm. Despite this cAMP spatial specificity, PKA activity was diffusely elevated throughout the 27 μm long dendrite. The lack of spatial specificity is due to diffusion of the molecule DARPP-32, which binds to the catalytic subunit of PKA, thereby impeding its inactivation. Because some experimental data suggests that PKA activity is limited in space[47], and the catalytic subunit of PKA is released from the anchored regulatory subunit to diffuse through the cytoplasm, this result suggests that other mechanisms for inactivation of PKA may be present. This mismatch between simulations and experiments is not necessarily a weakness of the model, rather a strength as it highlights and directs research to finding this critical, yet uncharacterized, mechanism for limiting the spatial domain of PKA activity.

The involvement of GPCRs coupled to the Gαq subtype of G protein in striatal synaptic plasticity is less straightforward: not only are they required for LTD, but also they may be involved in LTP. The phospholipase C activated by Gαq produces diacylglycerol[56], which is a required for both the endocannabinoid 2-arachidonyl glycerol (2AG), and protein kinase C[58]. A spatial model of these Gαq coupled pathways was developed to address the question of how temporal pattern of stimulation leads to either 2AG and LTD, or PKC and LTP[59] (Fig 3A). Simulations revealed that theta burst stimulation (which produces LTP) activated more PKC than 20 Hz stimulation (which produces LTD). More significantly, the properties of PKC binding to calcium and membrane diacylglycerol conveyed spatial specificity of PKC activity (Fig 3C). The lack of spatial specificity of 2AG (Fig 3B) suggested that diffuse LTD may provide heterosynaptic plasticity as a homeostatic mechanism. This model was verified with electrophysiology experiments demonstrating that PKC is required for theta burst LTP. A limitation of this model is the exclusion of the D1R coupled and other calcium activated signaling pathways; thus, several mechanisms of pathway interaction, such as CaMKII inhibition of diacylglycerol lipase[60] that may strengthen the difference between 20 Hz and theta burst, are not functioning in the model.

To investigate the question of spatial specificity in the cerebellum, a model of a dendrite with multiple spines[61] investigated whether geometrical factors, such as spine neck geometry, or biochemical factors could yield spatial specificity. Input to the model consisted of a pulse of inositol triphosphate (as produced by mGluR activation) in a single spine and

calcium influx to the spine and dendrite (as produce by depolarization). Simulations showed that inositol triphosphate does not reach appreciable concentration in the dendrite or nearby spines. The diffusional barrier of the spine neck (both to inositol triphosphate and to calcium) coupled with the high density and low sensitivity to calcium of the inositol triphosphate receptor creates a threshold situation that allowed calcium spikes to be restricted to the stimulated spines[61]. Thus, as spine neck diameter is increased 30% or more, calcium spikes are abolished. A limitation of this model is the use of deterministic simulations for phenomena occurring in spines, and the omission of signaling pathways downstream of calcium. The importance of stochastic phenomena is exhibited by a cerebellar model of the positive feedback loop of protein kinase C - MAPK - phospholipase A_2 leading to AMPA receptor phosphorylation and trafficking[62]. Simulations reveal that the number of synaptic AMPA receptors exhibits a bimodal distribution in small spines, suggesting that LTD is an all-or-none phenomenon, but a graded response both in large spines and in deterministic simulations. This result provides an outstanding example of how the dynamical behavior of a system depends on whether simulations are performed stochastically or deterministically, but a limitation is the restriction of this model to a single spine.

The mechanistic approach adopted by all these models allows specific predictions to be made, and in some cases tested experimentally. All models exhibit a trade-off between the complexity of signaling pathways and the spatial extent of the model. Indeed even the most elaborate signaling pathways are still a subset of the processes which allow convergent pathways to produce divergent responses, as has been observed in the ERK kinase cascade[63]. In addition, none of the models above simulated time frames (and processes) required for the protein synthesis dependent forms of synaptic plasticity relevant for long term memories. In the next section we highlight a few critical issues in synaptic plasticity that have been addressed with models of various degrees of complexity, but that remain unresolved.

CRITICAL ISSUES LIMITING OUR UNDERSTANDING OF NEURONAL SYNAPTIC PLASTICITY

What is the role of endocannabinoids in LTD?

Though the balance of CaMKII to calcineurin explains the direction of plasticity for homosynaptic plasticity in the hippocampus, other intracellular signaling pathways, such as endocannabinoids (eCBs) are involved in LTD in striatum, amygdala, neocortex, and cerebellum[64]. In such cases postsynaptic calcium influx together with stimulation of Gαq coupled receptors triggers the production of eCBs (either anandamide or 2AG), which diffuse in a retrograde direction across the postsynaptic membrane and synaptic cleft, and act on the presynaptic cannabinoid receptors[55] to cause a lasting inhibition of neurotransmitter release. In addition, observations on heterosynaptic LTD in the hippocampus demonstrate a requirement for eCBs[65], and also recent experiments[66] suggest that homosynaptic LTD in hippocampus induced by low frequency stimulation is generated by release of eCBs caused by a cooperative activation of NMDA receptors and type 5 metabotropic glutamate receptors.

Since production of eCBs requires calcium elevation, the question remains of how the spatio-temporal pattern of calcium controls direction of plasticity. One possibility is coincidence detection of Gαq coupled receptor stimulation and calcium elevation by phospholipase C[67]. In addition, the production of 2AG by diacylgylcerol lipase is enhanced by calcium elevation[68]. Because the dynamics of diacylgylcerol production[69], are considerably slower than the calcium transients produced by action potentials, coincidence

detection would appear to be optimized by glutamate stimulation occurring prior to an action potential, which is counter to the observation that LTD generally results when the action potential occurs first. For example, a calcium elevation produced by an action potential given subsequent to glutamate release may coincide with Gαq activation to optimize production of diacylglycerol, or the calcium may coincide with the elevation of diacylglycerol to optimize both production of 2AG and activation of PKC. In contrast, the calcium produced by an action potential give prior to glutamate release returns to basal level prior to the diacylglycerol elicited by subsequent glutamate release. Alternatively, the coincidence detectors involved in eCB dependent LTD may be optimized to low amplitude yet prolonged calcium dynamics. In other words, an action potential given prior to glutamate release may produce a lower amplitude but longer duration calcium elevation, whereas an action potential given after glutamate release may produce a higher amplitude but briefer calcium elevation[70]. Further modeling of the dynamics of calcium (especially that involved in calcium release), as well as of cross-talk between pathways, such as the CaMKII inhibition of diacylglycerol lipase[60] and the PKA enhancement of degradation of Gαq proteins[56], is required to understand temporal sensitivity of eCBs and their role in LTD.

What are critical targets of kinases for LTP and memory

How do the “memory” kinases, PKA, PKC, CaMKII and ERK1/2, produce LTP and synaptic plasticity? Because synaptic plasticity experiments measure the amplitude of the post-synaptic receptor response, a large body of research has focused on phosphorylation of the AMPA receptor by PKC and CaMKII on Ser831 and by PKA on Ser845 of the GluA1 subunit. Induction of long-term potentiation is accompanied by an increase in GluA1 phosphorylation on Ser831[71], and long-term depression is associated with dephosphorylation of Ser845[72]. The phosphorylation state of the receptor controls synaptic strength through cycling of the receptor in and out of the synapse[73], channel conductance[74] and channel open probability. Several models reproduce the change in AMPA channel conductance in response to stimulation conditions[13, 14, 75, 76], or even the role of structural synaptic proteins such as stargazin, SAP97 and PSD95 in AMPA receptor trafficking[15]. The limitation with the models of GluA1 phosphorylation is that Ser831A mutants still exhibit normal LTP and LTD[77].

A key observation for identifying critical targets of kinases is that long lasting forms of LTP and also long term memories require protein synthesis and transcription. What are the key kinase and phosphatase targets for initiating transcription and translation? During late phase long-term potentiation, both calcium and cAMP synergistically lead to phosphorylation of cAMP response element binding protein (CREB) on Ser133, which then binds to the cAMP response element (CRE) mediating gene transcription[78]. Several kinases either directly (PKA, PKC) or indirectly (ERK1/2) phosphorylate Ser133 of CREB, and deletion of CREB produces memory deficits in the hippocampus[79] and the striatum[80]. Histones are another class of molecules involved in transcription and keep the DNA in its inactive chromatin form. Histone regulation by methylation and adenylation is required to expose the DNA for transcription. CREB binding protein (CBP) functions as a histone acetyltransferase and when phosphorylated interacts with phosphorylated CREB[81]. Dominant negative expression of a mutant CBP in forebrain produced deficits of long lasting forms of LTP (L-LTP) and spatial memory[82]. Though the requirement for transcription and translation has long been known, the distance from the synapse to the nucleus makes this aspect of plasticity difficult to study computationally.

Evidence of local dendritic translation[83, 84] has inspired models of this aspect of synaptic plasticity. Translation initiation is controlled by the protein kinase S6 Kinase and eukaryotic initiation factor 4E , which are regulated by a signaling cascade initiated by BDNF[85]. Therefore, one approach is to develop a model of this cascade[86] together with the effect of

calcium on ERK1/2 phosphorylation. Model simulations showed that LTP and LTD stimuli can induce protein synthesis only in the presence of BDNF; however, the duration of protein synthesis was shorter than suggested by experiments, and bistability was not observed, suggesting that other mechanisms are involved in the maintenance of synaptic plasticity. Another control of translation is through polyadenylation of the tail of mRNA[87]. Cytoplasmic polyadenylation elements in the mRNA tail bind to a protein (CPEB1) which represses translation, and the phosphorylation of CPEB1 increases translation. A positive feedback loop is formed with CaMKII, which is synthesized locally and can phosphorylate CPEB1. The effect of this interaction on L-LTP was investigated in a computational model[88]. Simulations showed that this system can operate as a bistable switch, which is turned on by the calcium influx associated with LTP induction. An open question is how these two and perhaps other aspects of protein translation interact to produce long lasting forms of synaptic plasticity.

Since a neuron has only a single nucleus, this implies that transcription (and much of translation) cannot be specific to stimulated synapses. One hypothesis for achieving spatial specificity is known as synaptic tagging and capture[89]. In its simplest form, this hypothesis posits that induction of late phase synaptic plasticity triggers a non-specific production of plasticity-related-proteins, and that synaptic stimulation, which by itself may only produce the early phase of LTP, creates spatially specific “tags” which “capture” the plasticity-related-proteins. This hypothesis can explain how a weak stimulation, which by itself does not produce long lasting potentiation, can lead to long lasting potentiation when strong stimulation is applied to an independent set of synapses[90].

A few models have investigated mechanisms underlying synaptic tagging and capture. Despite the elegance of this theory, the identity of the synaptic tags remains unknown. One possibility is that the phosphorylation state of the synapse is the tag[91], as determined by several different kinases and phosphatases. Another possibility is that structural changes to the spine neck influence delivery of proteins to the spine. Indeed, though αCaMKII has been the focus of most previous studies, βCaMKII has been shown to be involved in assembly/disassembly of the actin[92] and a spatial, computational model shows that this influences protein mobility in the spine[93].

Two models of synaptic tagging and capture do not include detailed mechanisms of transcription or translation, instead they focus on the interaction between signals that initiate protein translation and signals that tag the synapse. A two compartment model of synaptic tagging and capture[94] investigated the interaction between CaMKII, another calcium activated kinase, PKMζ, and ERK1/2. Plasticity related proteins were synthesized in the dendritic compartment only if both the calcium activated kinase and ERK1/2 were sufficiently activated. These plasticity related proteins diffused into the synapse compartment but were “captured” only if the synapse had been tagged, either via CaMKII phosphorylation for LTP or by calcium activated phosphatases and ERK1/2 for LTD. Model simulations showed that LTP maintenance was caused by bistability in PKMζ activity. A more abstract yet stochastic model was developed to investigate cross-tagging[95], in which the induction of long lasting LTP can convert short duration LTD to long lasting LTD on an independent set of synapses. In this model, the timing of a pre-synaptic spike combined with post-synaptic depolarization determined the probability of a synapse to be tagged either for LTD or for LTP. Production of plasticity related proteins was initiated either if sufficient synapses had been tagged (which represents a strong induction protocol) or a high enough level of neuromodulator was present (e.g. dopamine). In the presence of plasticity related proteins, a tagged synapse could convert from short duration LTP to L-LTP or from short duration LTD to L-LTD. This model can account for various tagging and cross-tagging

phenomena. More concrete spatial models of synaptic tagging and capture must await additional experimental details about tag identity and control of protein synthesis.

How is ERK1/2 activated in neurons

Several of the models described above include activation of ERK1/2 via Raf kinase phosphorylation of mitogen activated protein kinase kinase, which then phosphorylates ERK1/2. Though this aspect is common to all ERK1/2 models, the activation of Raf kinase is rather diverse. The most common pathway forRaf kinase activation in non-neuronal cell models is through RTKs, adaptor proteins, guanosine exchange factors, and activation of Ras which then binds to and activates Raf kinase[26, 27, 96]. This pathway is activated by BDNF in neurons and is included in various models[86, 94, 97].

Synaptic plasticity experiments suggest that calcium influx can lead to ERK1/2 activation through several pathways in the absence of RTK activation. One of these pathways includes calcium activation of adenylyl cyclase and production of cAMP, followed by either PKA activation of ERK1/2[98], or cAMP binding to EPAC, which activates a different Ras family member, RapGTP[99]. A second pathway includes calcium binding to guanosine exchange factors, such as RasGRF[100, 101]. Though EPAC activation has been modeled[102], the activation of ERK1/2 by EPAC or by RasGRF has not been investigated in silico, but may be important in some forms of synaptic plasticity.

A third class of mechanism involves GPCRs in three different signaling pathways. The first involves Gαq coupled GPCRs, which lead to diacylglycerol that activates PKC and thus ERK1/2, as implemented in several models described above[49, 62]. A second, novel mechanism for GPCR activation of ERK1/2 is known as switching. Prolonged stimulation of Gαs coupled GPCRs leads to phosphorylation of these receptors, which not only decouples the receptor from the Gαs protein but can allow receptor activation of the Gαi type of protein[103]. Though the Gαi subunit inhibits adenylyl cyclase, the Giβγ subunits can recruit Src family kinases, which then recruit various adaptor proteins and guanosine exchange factors[104, 105]. The third signaling pathway is binding of arrestin to phosphorylated GPCRs without intervening Gαi activation. The ERK cascade can be activated directly via arrestin[39], which has been modeled[106] in non-neuronal cells. The question remains as to which of these mechanisms operates under which circumstances or in which cell types during induction of synaptic plasticity, and how anchoring proteins limit different pools of ERK to produce different physiological effects[63].

PARAMETER ESTIMATION AND SENSITIVITY ANALYSIS IN SPATIAL MODELS

The number of computer programs for computationally efficient simulation of large reaction-diffusion networks has been increasing, in concert with the increased computational power. Special purpose simulators used by the models discussed above include Vcell[107], GENESIS/Kinetikit/MOOSE[108, 109] which incorporates the Smoldyn algorithm[110] for stochastic simulation, STEPS[62], and NeuroRD[102]. Though these simulators differ in many aspects, the capabilities of all these simulators continue to be expanded, allowing increasingly complex models to be implemented. One difficulty that is independent of the simulator is that of parameter estimation and sensitivity analysis. Though parameter estimation has been incorporated into biochemical simulators such as Copasi[111], such approaches become exceedingly difficult in neural models for several reasons, most related to the spatial aspect of simulations. One problem is the lack of time course data for most molecules; however, new imaging techniques has produced a tremendous increase in necessary data with excellent temporal and spatial resolution[112]. Another is the simulation

time required for large scale spatial models – simulations requiring hours or days make most parameter search algorithms impractical. Compounding this last problem is the multiplicative increase in parameters when molecule concentrations can vary across compartments. Stepwise adjustment in parameters for distinct modules is the most common approach[112], but the tight coupling produced by multi-protein complexes makes difficult the translation from biochemical experiments to spatial neuron models.

CONCLUSION

The objective of this article was to review computational models that address spatial issues in synaptic plasticity. Several spatial models of signaling pathways have been developed to investigate the degree of spatial specificity of synaptic plasticity and the underlying mechanisms that contribute to (or hinder) spatial specificity. Molecular mechanisms that connect synaptic input to gene transcription and protein translation are intricately involved in formation of long term memories and synaptic plasticity; therefore, new mechanistic models of these phenomena must be developed hand-in-hand with experimental discoveries. Advances in live cell imaging coupled with software development for large scale simulations will continue to accelerate the development of spatial models of synaptic plasticity.

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Reference List

1. Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. Science. 2006; 313:1093–1097. [PubMed: 16931756]
2. Yin HH, et al. Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. Nat. Neurosci. 2009; 12:333–341. [PubMed: 19198605]
3. O'Dell TJ, Connor SA, Gelinas JN, Nguyen PV. Viagra for your synapses: Enhancement of hippocampal long-term potentiation by activation of beta-adrenergic receptors. Cell Signal. 2010; 22:728–736. [PubMed: 20043991]
4. Bliss TVP, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993; 361:31–39. [PubMed: 8421494]
5. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron. 2004; 44:5–21. [PubMed: 15450156]
6. Fino E, et al. Distinct coincidence detectors govern the corticostriatal spike timing-dependent plasticity. J. Physiol. 2010; 588:3045–3062. [PubMed: 20603333]
7. Adermark L, Lovinger DM. Combined activation of L-type Ca2+ channels and synaptic transmission is sufficient to induce striatal long-term depression. J Neurosci. 2007; 27:6781–6787. [PubMed: 17581965]
8. Khodakhah K, Armstrong CM. Induction of long-term depression and rebound potentiation by insitol triphosphate in cerebellar purkinje neurons. Proc. Natl. Acad. Sci. U. S. A. 1997; 94:14009–14014. [PubMed: 9391143]
9. Faas GC, Raghavachari S, Lisman JE, Mody I. Calmodulin as a direct detector of Ca(2+) signals. Nat. Neurosci. 2011; 14:301–304. [PubMed: 21258328]
10. Lisman J, Yasuda R, Raghavachari S. Mechanisms of CaMKII action in long-term potentiation. Nat. Rev. Neurosci. 2012; 13:169–182. [PubMed: 22334212]
11. Mulkey RM, Endo S, Shenolikar S, Malenka RC. Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. Nature. 1994; 369:486–488. [PubMed: 7515479]

12. Roche KW, O'Brien RJ, Mammen AL, Bernhardt J, Huganir RL. Characterization of multiple phosphorylation sites on the AMPA receptor GluR1 subunit. Neuron. 1996; 16:1179–1188. [PubMed: 8663994]
13. Graupner M, Brunel N. STDP in a bistable synapse model based on CaMKII and associated signaling pathways. PLoS. Comput. Biol. 2007; 3:e221. [PubMed: 18052535]
14. Castellani GC, Quinlan EM, Bersani F, Cooper LN, Shouval HZ. A model of bidirectional synaptic plasticity: from signaling network to channel conductance. Learn. Mem. 2005; 12:423–432. [PubMed: 16027175]
15. Zhabotinsky AM, Camp RN, Epstein IR, Lisman JE. Role of the neurogranin concentrated in spines in the induction of long-term potentiation. J Neurosci. 2006; 26:7337–7347. [PubMed: 16837580]
16. Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J. Neurosci. 1992; 12:4224–4233. [PubMed: 1359031]
17. Wickens JR, Begg AJ, Arbuthnott GW. Dopamine reverses the depression of rat corticostriatal synapses which normally follows high-frequency stimulation of cortex in vitro. Neuroscience. 1996; 70:1–5. [PubMed: 8848115]
18. Ito M. Cerebellar long-term depression: characterization, signal transduction, and functional roles. Physiol Rev. 2001; 81:1143–1195. [PubMed: 11427694]
19. Spencer JP, Murphy KP. Activation of cyclic AMP-dependent protein kinase is required for long-term enhancement at corticostriatal synapses in rats. Neurosci. Lett. 2002; 329:217–221. [PubMed: 12165416]
20. Abel T, et al. Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. Cell. 1997; 88:615–626. [PubMed: 9054501]
21. Howard AD, et al. Orphan G-protein-coupled receptors and natural ligand discovery. Trends Pharmacol. Sci. 2001; 22:132–140. [PubMed: 11239576]
22. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog. Neurobiol. 2005; 76:99–125. [PubMed: 16099088]
23. Kao S, Jaiswal RK, Kolch W, Landreth GE. Identification of the mechanisms regulating the differential activation of the mapk cascade by epidermal growth factor and nerve growth factor in PC12 cells. J. Biol. Chem. 2001; 276:18169–18177. [PubMed: 11278445]
24. Luttrell LM. Composition and function of g protein-coupled receptor signalsomes controlling mitogen-activated protein kinase activity. J. Mol. Neurosci. 2005; 26:253–264. [PubMed: 16012199]
25. Milligan G, Kostenis E. Heterotrimeric G-proteins: a short history. Br. J. Pharmacol. 2006; 147(Suppl.1):S46–S55. [PubMed: 16402120]
26. Kholodenko BN. Cell-signalling dynamics in time and space. Nat. Rev. Mol. Cell Biol. 2006; 7:165–176. [PubMed: 16482094]
27. Sasagawa S, Ozaki Y, Fujita K, Kuroda S. Prediction and validation of the distinct dynamics of transient and sustained ERK activation. Nat. Cell Biol. 2005; 7:365–373. [PubMed: 15793571]
28. Tanaka K, Augustine GJ. A positive feedback signal transduction loop determines timing of cerebellar long-term depression. Neuron. 2008; 59:608–620. [PubMed: 18760697]
29. Hirono M, et al. Phospholipase Cbeta4 and protein kinase Calpha and/or protein kinase CbetaI are involved in the induction of long term depression in cerebellar Purkinje cells. J. Biol. Chem. 2001; 276:45236–45242. [PubMed: 11551922]
30. Dremier S, Kopperud R, Doskeland SO, Dumont JE, Maenhaut C. Search for new cyclic AMP-binding proteins. FEBS Lett. 2003; 546:103–107. [PubMed: 12829244]
31. Houslay MD, Adams DR. PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. Biochem. J. 2003; 370:1–18. [PubMed: 12444918]
32. Vecsey CG, et al. Sleep deprivation impairs cAMP signalling in the hippocampus. Nature. 2009; 461:1122–1125. [PubMed: 19847264]

33. Navakkode S, Sajikumar S, Frey JU. The type IV-specific phosphodiesterase inhibitor rolipram and its effect on hippocampal long-term potentiation and synaptic tagging. J Neurosci. 2004; 24:7740–7744. [PubMed: 15342741]
34. Bhalla US. The chemical organization of signaling interactions. Bioinformatics. 2002; 18:855–863. [PubMed: 12075021]
35. Ferrell JE Jr. Self-perpetuating states in signal transduction: positive feedback, double-negative feedback and bistability. Curr. Opin. Cell Biol. 2002; 14:140–148. [PubMed: 11891111]
36. Bi GQ, Rubin J. Timing in synaptic plasticity: from detection to integration. Trends Neurosci. 2005; 28:222–228. [PubMed: 15866196]
37. Woo NH, Duffy SN, Abel T, Nguyen PV. Temporal spacing of synaptic stimulation critically modulates the dependence of LTP on cyclic AMP-dependent protein kinase. Hippocampus. 2003; 13:293–300. [PubMed: 12699336]
38. Kim M, Huang T, Abel T, Blackwell KT. Temporal sensitivity of protein kinase a activation in late-phase long term potentiation. PLoS. Comput. Biol. 2010; 6:e1000691. [PubMed: 20195498]
39. Ahn S, Shenoy SK, Wei H, Lefkowitz RJ. Differential kinetic and spatial patterns of beta-arrestin and G protein-mediated ERK activation by the angiotensin II receptor. J. Biol. Chem. 2004; 279:35518–35525. [PubMed: 15205453]
40. Irvine JM, Blackwell KT, Alkon DL, Vogl TP. Angular separation in neural networks. J. Artificial. Neural Networks. 1994; 1:169–182.
41. Barrett AB, van Rossum MC. Optimal learning rules for discrete synapses. PLoS. Comput. Bio. 2008; l4:e1000230. [PubMed: 19043540]
42. Harvey CD, Svoboda K. Locally dynamic synaptic learning rules in pyramidal neuron dendrites. Nature. 2007; 450:1195–1200. [PubMed: 18097401]
43. Biess A, Korkotian E, Holcman D. Barriers to diffusion in dendrites and estimation of calcium spread following synaptic inputs. PLoS. Comput. Bio. 2011; l7:e1002182. [PubMed: 22022241]
44. Wong W, Scott JD. AKAP signalling complexes: focal points in space and time. Nat. Rev. Mol. Cell Biol. 2004; 5:959–970. [PubMed: 15573134]
45. Ostroveanu A, et al. A-kinase anchoring protein 150 in the mouse brain is concentrated in areas involved in learning and memory. Brain Res. 2007; 1145:97–107. [PubMed: 17321504]
46. Havekes R, et al. Gravin orchestrates protein kinase A and beta2-adrenergic receptor signaling critical for synaptic plasticity and memory. J. Neurosci. 2012; 32:18137–18149. [PubMed: 23238728]
47. Cantrell AR, Tibbs VC, Westenbroek RE, Scheuer T, Catterall WA. Dopaminergic modulation of voltage-gated Na+ current in rat hippocampal neurons requires anchoring of cAMP-dependent protein kinase. J. Neurosci. 1999; 19:RC21. [PubMed: 10460275]
48. Zaccolo M. Phosphodiesterases and compartmentalized cAMP signalling in the heart. Eur. J. Cell Biol. 2006
49. Ajay SM, Bhalla US. A propagating ERKII switch forms zones of elevated dendritic activation correlated with plasticity. HFSP. J. 2007; 1:49–66. [PubMed: 19404460]
50. Neves SR, et al. Cell shape and negative links in regulatory motifs together control spatial information flow in signaling networks. Cell. 2008; 133:666–680. [PubMed: 18485874]
51. Bhalla US. Multiscale interactions between chemical and electric signaling in LTP induction, LTP reversal and dendritic excitability. Neural Netw. 2011; 24:943–949. [PubMed: 21616637]
52. Nie T, McDonough CB, Huang T, Nguyen PV, Abel T. Genetic disruption of protein kinase A anchoring reveals a role for compartmentalized kinase signaling in theta-burst long-term potentiation and spatial memory. J. Neurosci. 2007; 27:10278–10288. [PubMed: 17881534]
53. Kim M, et al. Colocalization of PKA with adenylyl cyclase enhances PKA activity during L-LTP induction. PLoS Comput Biol. 2011; 7:e1002085. [PubMed: 21731481]
54. Herve D, et al. G(olf) and Gs in rat basal ganglia: possible involvement of G(olf) in the coupling of dopamine D1 receptor with adenylyl cyclase. J. Neurosci. 1993; 13:2237–2248. [PubMed: 8478697]
55. Gerdeman GL, Ronesi J, Lovinger DM. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. Nat. Neurosci. 2002; 5:446–451. [PubMed: 11976704]

56. Lerner TN, Kreitzer AC. RGS4 Is Required for Dopaminergic Control of Striatal LTD and Susceptibility to Parkinsonian Motor Deficits. Neuron. 2012; 73:347–359. [PubMed: 22284188]
57. Oliveira RF, Kim M, Blackwell KT. Subcellular Location of PKA Controls Striatal Plasticity: Stochastic Simulations in Spiny Dendrites. PLoS Comput Biol. 2012; 8:e1002383. [PubMed: 22346744]
58. Oancea E, Meyer T. Protein kinase C as a molecular machine for decoding calcium and diacylglycerol signals. Cell. 1998; 95:307–318. [PubMed: 9814702]
59. Kim B, Hawes SL, Gillani F, Wallace LJ, Blackwell KT. Signaling Pathways Involved in Striatal Synaptic Plasticity are Sensitive to Temporal Pattern and Exhibit Spatial Specificity. PLoS. Comput. Biol. 2013; 9:e1002953. [PubMed: 23516346]
60. Shonesy BC, et al. CaMKII regulates diacylglycerol lipase-alpha and striatal endocannabinoid signaling. Nat. Neurosci. 2013; 16:456–463. [PubMed: 23502535]
61. Hernjak N, et al. Modeling and analysis of calcium signaling events leading to long-term depression in cerebellar Purkinje cells. Biophys. J. 2005; 89:3790–3806. [PubMed: 16169982]
62. Antunes G, De SE. A stochastic signaling network mediates the probabilistic induction of cerebellar long-term depression. J. Neurosci. 2012; 32:9288–9300. [PubMed: 22764236]
63. Shalin SC, Hernandez CM, Dougherty MK, Morrison DK, Sweatt JD. Kinase suppressor of Ras1 compartmentalizes hippocampal signal transduction and subserves synaptic plasticity and memory formation. Neuron. 2006; 50:765–779. [PubMed: 16731514]
64. Chevaleyre V, Takahashi KA, Castillo PE. Endocannabinoid-mediated synaptic plasticity in the CNS. Annu. Rev. Neurosci. 2006; 29:37–76. [PubMed: 16776579]
65. Yasuda H, Huang Y, Tsumoto T. Regulation of excitability and plasticity by endocannabinoids and PKA in developing hippocampus. Proc. Natl. Acad. Sci. U. S. A. 2008; 105:3106–3111. [PubMed: 18287074]
66. Izumi Y, Zorumski CF. NMDA receptors, mGluR5, and endocannabinoids are involved in a cascade leading to hippocampal long-term depression. Neuropsychopharmacology. 2012; 37:609–617. [PubMed: 21993209]
67. Rack M, Xhonneux-Cremers B, Schraermeyer U, Stieve H. On the Ca^{2+} dependence of insitol-phospholid-specific phospholipase C of micovillar photoreceptors from sepia officinalis. Exp. Eye Res. 1994; 58:659–664. [PubMed: 7925705]
68. Bisogno T, et al. Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. J. Cell Biol. 2003; 163:463–468. [PubMed: 14610053]
69. Hashimotodani Y, Ohno-Shosaku T, Watanabe M, Kano M. Roles of phospholipase Cbeta and NMDA receptor in activity-dependent endocannabinoid release. J. Physiol. 2007; 584:373–380. [PubMed: 17615097]
70. Keller DX, Franks KM, Bartol TM Jr, Sejnowski TJ. Calmodulin activation by calcium transients in the postsynaptic density of dendritic spines. PLoS. ONE. 2008; 3:e2045. [PubMed: 18446197]
71. Barria A, Muller D, Derkach V, Griffith LC, Soderling TR. Regulatory phosphorylation of AMPA-type glutamate receptors by CaM-KII during long-term potentiation. Science. 1997; 276:2042–2044. [PubMed: 9197267]
72. Lee HK, Kameyama K, Huganir RL, Bear MF. NMDA induces long-term synaptic depression and dephosphorylation of the GluR1 subunit of AMPA receptors in hippocampus. Neuron. 1998; 21:1151–1162. [PubMed: 9856470]
73. Esteban JA, et al. PKA phosphorylation of AMPA receptor subunits controls synaptic trafficking underlying plasticity. Nat. Neurosci. 2003; 6:136–143. [PubMed: 12536214]
74. Derkach V, Barria A, Soderling TR. Ca2+/calmodulin-kinase II enhances channel conductance of alpha-amino-3- hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. Proc. Natl. Acad. Sci. U. S. A. 1999; 96:3269–3274. [PubMed: 10077673]
75. Castellani GC, Quinlan EM, Cooper LN, Shouval HZ. A biophysical model of bidirectional synaptic plasticity: dependence on AMPA and NMDA receptors. Proc. Natl. Acad. Sci. U. S. A. 2001; 98:12772–12777. [PubMed: 11675507]
76. Nakano T, Doi T, Yoshimoto J, Doya KA. kinetic model of dopamine- and calcium-dependent striatal synaptic plasticity. PLoS Comput. Biol. 2010; 6:e1000670. [PubMed: 20169176]

77. Lee HK, Takamiya K, He K, Song L, Huganir RL. Specific roles of AMPA receptor subunit GluR1 (GluA1) phosphorylation sites in regulating synaptic plasticity in the CA1 region of hippocampus. J. Neurophysiol. 2010; 103:479–489. [PubMed: 19906877]
78. Impey S, et al. Induction of CRE-mediated gene expression by stimuli that generate long-lasting LTP in area CA1 of the hippocampus. Neuron. 1996; 16:973–982. [PubMed: 8630255]
79. Pittenger C, et al. Reversible inhibition of CREB/ATF transcription factors in region CA1 of the dorsal hippocampus disrupts hippocampus-dependent spatial memory. Neuron. 2002; 34:447–462. [PubMed: 11988175]
80. Pittenger C, et al. Impaired bidirectional synaptic plasticity and procedural memory formation in striatum-specific cAMP response element-binding protein-deficient mice. J Neurosci. 2006; 26:2808–2813. [PubMed: 16525060]
81. McManus KJ, Hendzel MJ. CBP, a transcriptional coactivator and acetyltransferase. Biochem. Cell Biol. 2001; 79:253–266. [PubMed: 11467739]
82. Wood MA, et al. Transgenic mice expressing a truncated form of CREB-binding protein (CBP) exhibit deficits in hippocampal synaptic plasticity and memory storage. Learn. Mem. 2005; 12:111–119. [PubMed: 15805310]
83. Bramham CR, Wells DG. Dendritic mRNA: transport, translation and function. Nat. Rev. Neurosci. 2007; 8:776–789. [PubMed: 17848965]
84. Kang H, Schuman EM. A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. Science. 1996; 273:1402–1406. [PubMed: 8703078]
85. Kang H, Schuman EM. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science. 1995; 267:1658–1662. 1658–1662. [PubMed: 7886457]
86. Jain P, Bhalla US. Signaling logic of activity-triggered dendritic protein synthesis: an mTOR gate but not a feedback switch. PLoS. Comput. Biol. 2009; 5:e1000287. [PubMed: 19242559]
87. Wells DG, et al. A role for the cytoplasmic polyadenylation element in NMDA receptor-regulated mRNA translation in neurons. J. Neurosci. 2001; 21:9541–9548. [PubMed: 11739565]
88. Aslam N, Kubota Y, Wells D, Shouval HZ. Translational switch for long-term maintenance of synaptic plasticity. Mol. Syst. Biol. 2009; 5: 284. [PubMed: 19536207]
89. Sajikumar S, Frey JU. Late-associativity, synaptic tagging, and the role of dopamine during LTP and LTD. Neurobiol. Learn. Mem. 2004; 82:12–25. [PubMed: 15183167]
90. Parvez S, Ramachandran B, Frey JU. Functional differences between and across different regions of the apical branch of hippocampal CA1 dendrites with respect to long-term depression induction and synaptic cross-tagging. J. Neurosci. 2010; 30:5118–5123. [PubMed: 20371832]
91. Redondo RL, Morris RG. Making memories last: the synaptic tagging and capture hypothesis. Nat. Rev. Neurosci. 2011; 12:17–30. [PubMed: 21170072]
92. Ramachandran B, Frey JU. Interfering with the actin network and its effect on long-term potentiation and synaptic tagging in hippocampal CA1 neurons in slices in vitro. J. Neurosci. 2009; 29:12167–12173. [PubMed: 19793974]
93. Khan S, et al. Sequestration of CaMKII in dendritic spines in silico. J. Comput Neurosci. 2011; 31:581–594. [PubMed: 21491127]
94. Smolen P, Baxter DA, Byrne JH. Molecular constraints on synaptic tagging and maintenance of long-term potentiation: a predictive model. PLoS. Comput. Biol. 2012; 8:e1002620. [PubMed: 22876169]
95. Clopath C, Ziegler L, Vasilaki E, Busing L, Gerstner W. Tag-trigger-consolidation: a model of early and late long-term-potentiation and depression. PLoS. Comput. Biol. 2008; 4:e1000248. [PubMed: 19112486]
96. Cirit M, Wang CC, Haugh JM. Systematic quantification of negative feedback mechanisms in the extracellular signal-regulated kinase (ERK) signaling network. J. Biol Chem. 2010; 285:36736–36744. [PubMed: 20847054]
97. Bhalla US, Iyengar R. Emergent properties of networks of biological signaling pathways. Science. 1999; 283:381–387. [PubMed: 9888852]
98. Sindreu CB, Scheiner ZS, Storm DR. Ca2+ -stimulated adenylyl cyclases regulate ERK-dependent activation of MSK1 during fear conditioning. Neuron. 2007; 53:79–89. [PubMed: 17196532]

99. Wang Z, et al. Rap1-mediated activation of extracellular signal-regulated kinases by cyclic AMP is dependent on the mode of Rap1 activation. Mol. Cell Biol. 2006; 26:2130–2145. [PubMed: 16507992]
100. Yasuda R, et al. Supersensitive Ras activation in dendrites and spines revealed by two-photon fluorescence lifetime imaging. Nat. Neurosci. 2006; 9:283–291. [PubMed: 16429133]
101. Fasano S, et al. Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) controls activation of extracellular signal-regulated kinase (ERK) signaling in the striatum and long-term behavioral responses to cocaine. Biol Psychiatry. 2009; 66:758–768. [PubMed: 19446794]
102. Oliveira RF, et al. The role of type 4 phosphodiesterases in generating microdomains of cAMP: large scale stochastic simulations. PLoS One. 2010; 5:e11725. [PubMed: 20661441]
103. Martin NP, Whalen EJ, Zamah MA, Pierce KL, Lefkowitz RJ. PKA-mediated phosphorylation of the beta1-adrenergic receptor promotes Gs/Gi switching. Cell Signal. 2004; 16:1397–1403. [PubMed: 15381255]
104. Luttrell LM, et al. Role of c-Src tyrosine kinase in G protein-coupled receptor- and Gbetagamma subunit-mediated activation of mitogen-activated protein kinases. J. Biol. Chem. 1996; 271:19443–19450. [PubMed: 8702633]
105. Della Rocca GJ, et al. Ras-dependent mitogen-activated protein kinase activation by G protein-coupled receptors Convergence of Gi- and Gq-mediated pathways on calcium/calmodulin, Pyk2, and Src kinase. J. Biol. Chem. 1997; 272:19125–19132. [PubMed: 9235901]
106. Heitzler D, et al. Competing G protein-coupled receptor kinases balance G protein and beta-arrestin signaling. Mol. Syst. Biol. 2012; 8:590. [PubMed: 22735336]
107. Moraru II, et al. Virtual Cell modelling and simulation software environment. IET. Syst. Biol. 2008; 2:352–362. [PubMed: 19045830]
108. Bower, JM.; Beeman, D. The Book of Genesis: Exploring Realistic Neural Models with the GEneral NEural SImulation System. New York: Springer-Verlag; 1998.
109. Ray S, Bhalla US. PyMOOSE: Interoperable Scripting in Python for MOOSE. Front Neuroinformatics. 2008; 2:6.
110. Andrews SS, Addy NJ, Brent R, Arkin AP. Detailed simulations of cell biology with Smoldyn 2.1. PLoS Comput. Biol. 2010; 6:e1000705. [PubMed: 20300644]
111. Sahle S, Mendes P, Hoops S, Kummer U. A new strategy for assessing sensitivities in biochemical models. Philos. Transact. A Math. Phys. Eng Sci. 2008; 366:3619–3631.
112. Neves SR. Modeling of spatially-restricted intracellular signaling. Wiley. Interdiscip. Rev. Syst. Biol. Med. 2012; 4:103–115. [PubMed: 21766466]

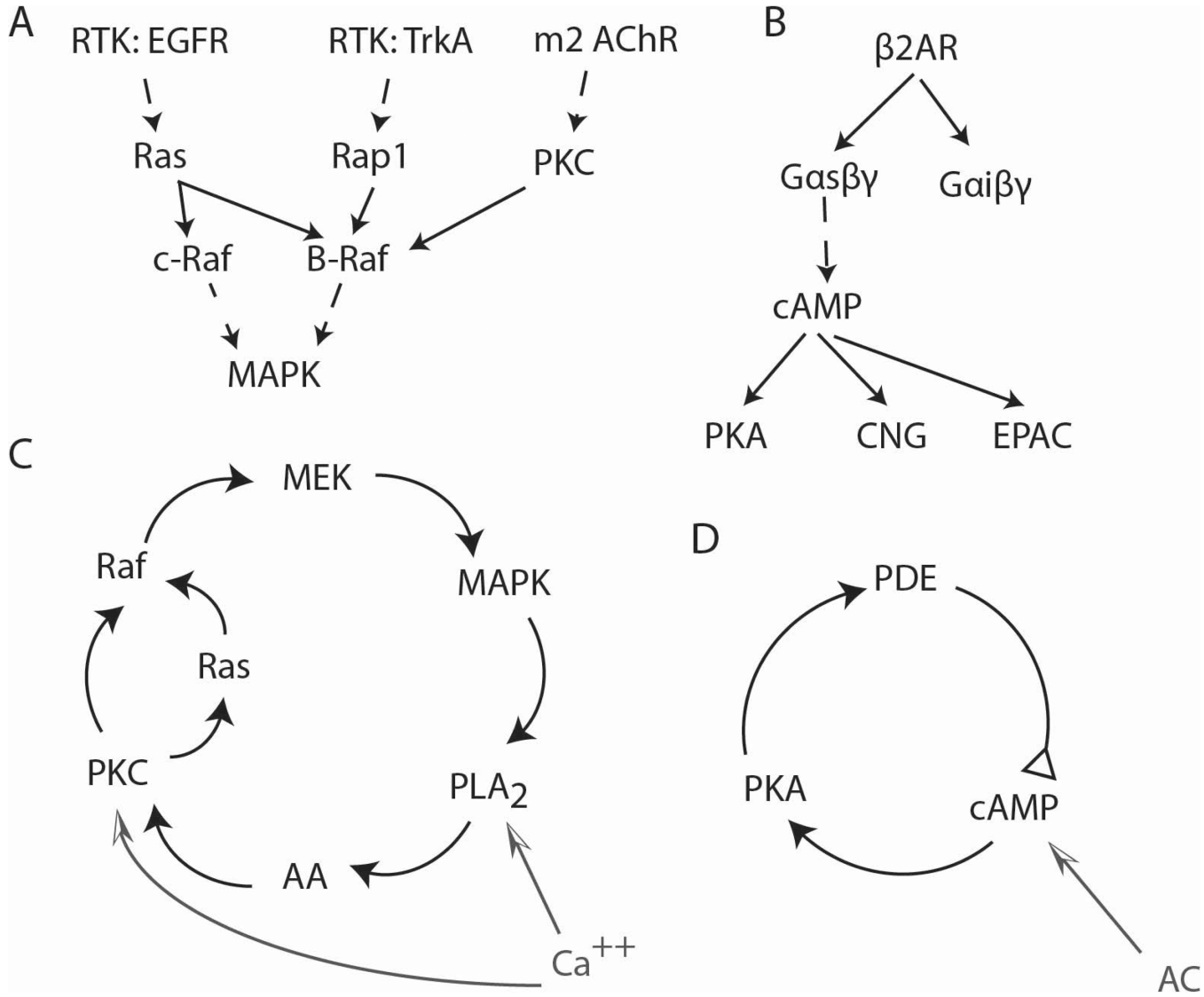

Fig 1.

Divergence, convergence, positive and negative feedback loops. (A) Convergence from various transmembrane receptors to MAPK phosphorylation. (B) Divergence from βAR activation to multiple downstream effectors. The β-adrenergic receptor is coupled to the Gαs type of G protein, but phosphorylation by protein kinase A (PKA) switches the association of the receptor from Gαs to the Gαi subtype of G protein [103]. The cAMP produced by adenylyl cyclase can activate PKA, EPAC or cyclic nucleotide gated channels (CNG). (C) Positive feedback loop in which MAPK activates PLA_2 via phosphorylation, PLA_2 produces arachidonic acid which activates PKC, and PKC phosphorylation of both Raf and Ras activate MAPK (D) Negative feedback loop involving PKA, phosphodiesterase type 4 (PDE4) and cAMP. A dashed line indicates that several intermediaries have been omitted.

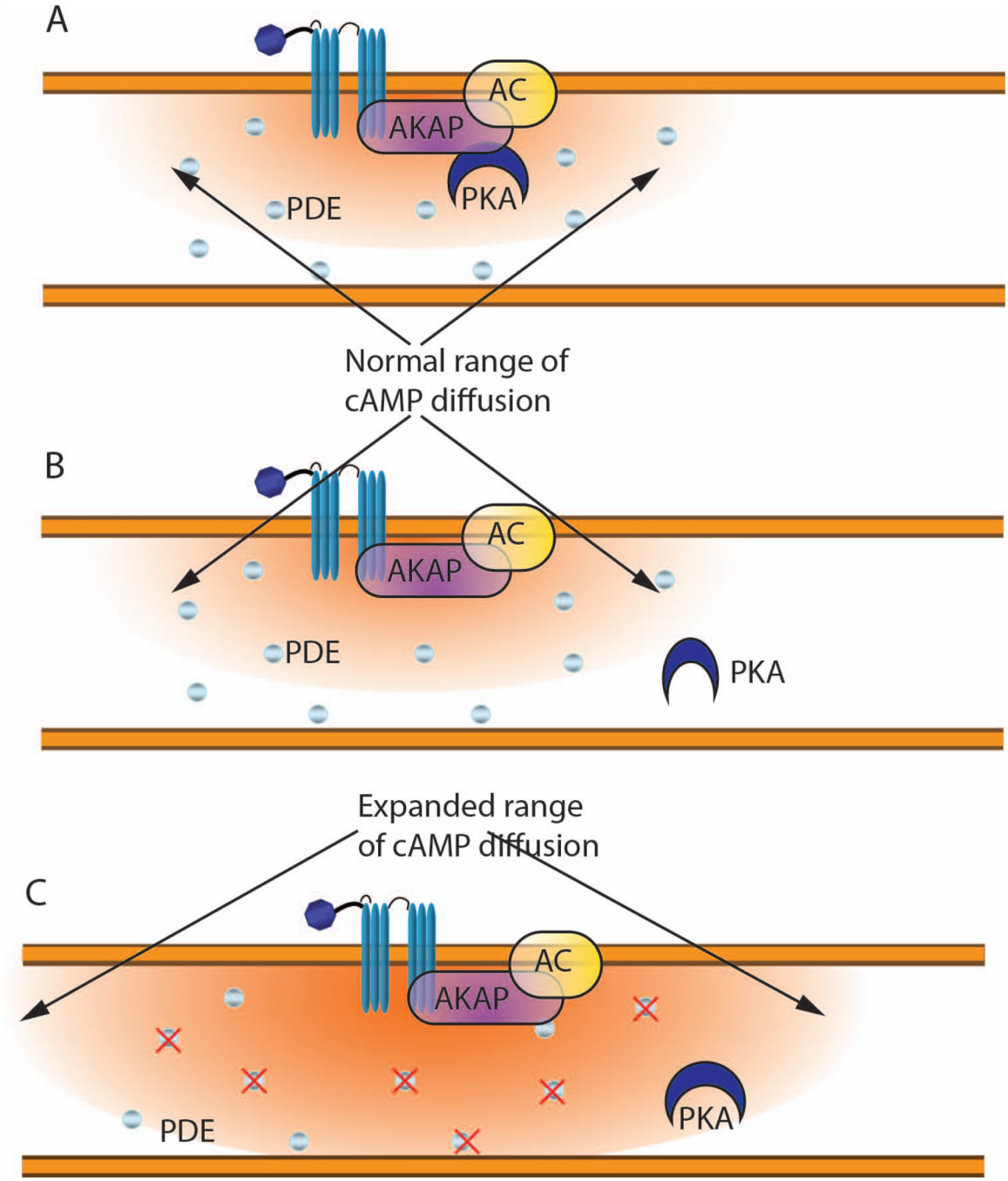

Fig 2.

Spatial aspect of signaling molecules in neurons. A. The diffusional distance of cAMP produced by adenylyl cyclase (AC) is limited by degradation by various phosphodiesterase (PDE) isosforms. Due to this steep concentration gradient, PKA needs to be anchored near the adenylyl cyclase for activation. B. When anchoring of PKA is blocked, it resides outside of the domain of high cAMP concentration, and thus its activation is decreased. (C) When phosphodiesterases are blocked, cAMP diffuses further and the spatial gradient of cAMP is reduced, demonstrating the role of inactivation mechanisms for spatial gradients. A reduced spatial gradient lessens the need for PKA to be located near the site of cAMP production; thus, PKA can be activated even if not anchored near the adenylyl cyclase.

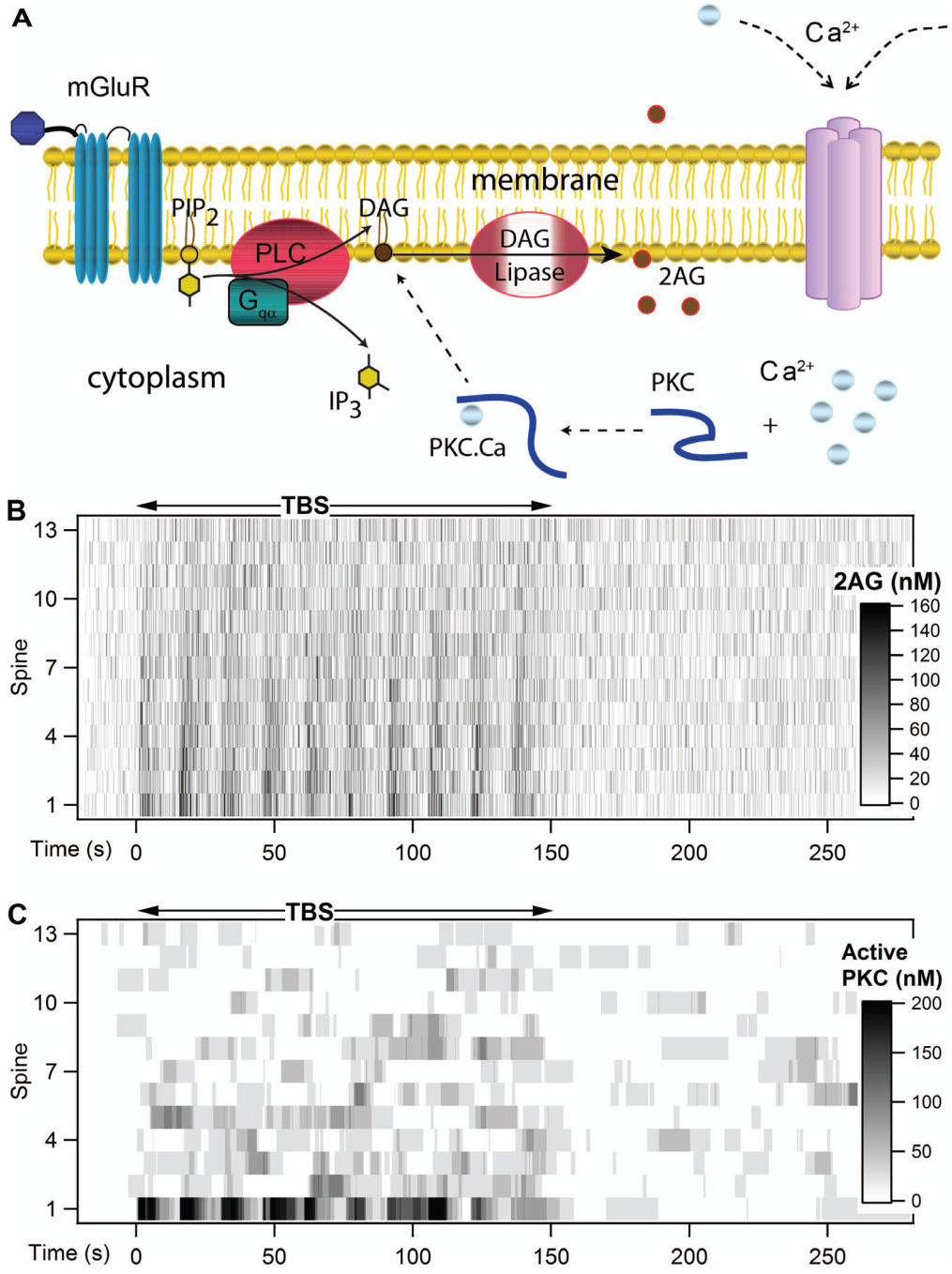

Fig 3.

Spatial specificity in a striatal model of PKC and 2AG activation. (A) Calcium influx occurs through either NMDA receptors or voltage gated calcium channels. The Gαq coupled metabotropic glutamate receptors are activated by glutamate binding. Gαq binding to phospholipase C leads to production of DAG. PKC is activated via calcium binding followed by DAG binding. 2AG is produced from DAG by DAG lipase. These pathways are implemented in a dendrite with 13 spines. The molecules associated with the membrane do not diffuse, but molecules shown in the cytoplasm diffuse freely. (B) Spatial specificity of PKC, but not 2AG (C), is observed in response to theta burst stimulation (TBS). Input to the model consisted of a moderate calcium influx to the dendrite (representing neuron

depolarization) and a larger calcium influx plus glutamate release to spine 1, representing synaptic activation of spine 1. This input was repeated in a theta burst pattern. Modified from[59]