Mechanisms for Antagonistic Regulation of AMPA and NMDA-D1 Receptor Complexes at Postsynaptic Sites

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1 The problem: Maintenance of stable states

The difficulty of clearly establishing a mechanism for LTP/LTD has been sometimes analyzed as stemming from its definition as an electrophysiological phenomenon corresponding to a number of different molecular components of both presynaptic and postsynaptic plasticity regulation.

Here we present a hypothesis on the pathways underlying AMPAR/D1R regulation derived from an ongoing project on modeling membrane receptor plasticity[3]. We assume that the maintenance of brief or repetitive input signals at membrane receptors necessary to achieve lasting receptor upregulation is mainly supported by the interactive dynamics of the intracellular system, rather than being located in individual switches. Here we suggest specifically a bifurcation into two stable states for a simulated cortico-striatal synapse (Fig. 1). This model incorporates the important role of calcium dynamics and the CaMKII autophosphorylation switch but emphasizes the increased computational power achieved by cAMP-calcium interaction and dopamine D1 receptors (or other G-protein coupled receptors located at postsynaptic sites).

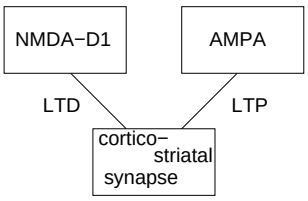

Figure 1: Two stable states for postsynaptic receptor regulation

2 cAMP-dependent modulation of calcium signals

The interaction of cAMP and calcium is a major factor in determining activation levels of a number of proteins critically involved in synaptic plasticity (see 3). Receptor complexes involving D1R and L-type calcium channels produce cAMP elevation at receptor activation and calcium influx through opening of the L-type calcium channels, where calcium further raises cAMP via the calcium-activated adenylyl cyclases AC1 and AC8. (The synergistic cAMP/calcium signal can be terminated by G_i coupled receptors, e.g. μ-opioid or dopamine D2 receptors.) NMDA receptor activation by high-frequency glutamatergic stimulation can produce sharp calcium signals sufficient to induce AMPA upregulation and LTP, e.g. in hippocampal CA1/CA3 but also at corticostriatal synapses. However, a different induction pattern, favoring longer lasting, weaker calcium oscillations induces AMPA LTD in hippocampus, which is also the dominant effect with dopamine D1 receptor stimulation at corticostriatal synapses.

A simulation of cAMP/calcium interaction shows that cAMP activation generates broadened oscillatory calcium signals (a) because of the sustained feedback between cAMP and calcium and (b) because cAMP is highly diffusible, and in spite of some compartmentalization of the signal will extend beyond the limits of a single synapse. Both effects counteract the generation of very high concentration gradients for calcium.

This means that the concurrent or temporally contiguous activation of cAMP during NMDA receptor mediated calcium entry is capable of profoundly altering the calcium signal and prevent the kind of persistent AMPA phosphorylation required for LTP-like AMPA upregulation.

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3 Regulation of AMPA and D1 receptor efficacy

The analysis of the kinase-phosphatase regulatory network stimulated by NMDA, AMPA and dopamine receptors shows the emergence of two internally consistent states of protein phosphorylation state and concentration (see Fig. 2A and Fig. 2B).

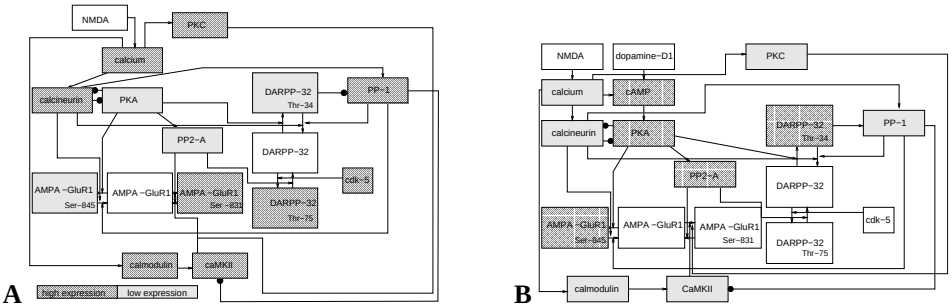

Figure 2: Intracellular Network for AMPA **(A)** and NMDA-D1 **(B)** dominated synapse

CaMKII is the autophosphorylated switch that gets turned on by high calcium. It promotes AMPA-gluR1-Ser-831 phosphorylation, which seems to be the dominant mode for the induction of AMPA up-regulation and LTP. Calcineurin dephosphorylates AMPA-gluR1-Ser-845 and in this way lowers AMPA peak current. High calcineurin and low PP2-A concentrations also impair dopamine signaling pushing DARPP-32 into a Thr-75 phosphorylated state. This removes inhibition of PP-1 and allows PP-1 regulation of the CaMKII switch to operate. High cdk5 can inhibit NMDA currents, and thus may prevent further plasticity (Fig. 2A).

With cAMP activation, PKA and PP2-A are highly activated, while calcineurin/PP-1 are low. AMPA is predominantly phosphorylated by PKA at Ser-845 and dephosphorylated at Ser-831 which induces increase of peak current but may prevent lasting plasticity. In contrast the DARPP-32 switch at Thr-34, together with the slow calcium oscillation promotes D1 receptor insertion (Fig. 2B).

These states are both robust and stable, they do not contain major instabilities, thus they are suitable for the maintenance of input signals and induction of longer-term plasticity, such as receptor endo- and exocytosis. The proposed model relates to a number of attested observations:

- NMDA activation and prolonged calcium increase promotes D1 insertion
- D1 receptor activation promotes AMPA desensitization/downregulation (LTD), but increases AMPA peak current
- high-frequency stimulation induces LTP, requiring CaMKII autophosphorylation
- maintenance of LTP-state is associated with NMDA downregulation and reduction of calcium inflow.

4 Conclusion

From the analysis of these pathways we conclude that postsynaptic processes that regulate synaptic transmission undergo significant cross-talk with respect to glutamatergic and neuromodulatory (dopamine) signals. The main hypothesis is that of a compensatory regulation, a competitive switch between the induction of increased AMPA conductance by CaMKII-dependent phosphorylation and reduced expression of PP2A, and increased D1 receptor sensitivity and expression by increased PKA, PP2A and decreased PP-1/calcineurin expression. Both types of plasticity are induced by NMDA receptor activation and increased internal calcium, they require different internal conditions to become expressed. Specifically, we propose that AMPA regulation and D1 regulation are inversely coupled. The net result may be a bifurcation of synaptic state into predominantly AMPA or NMDA-D1 synapses. This could have functional consequences: stable connections for AMPA and conditional gating for NMDA-D1 synapses.