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Simulations suggest pharmacological methods for rescuing long-term potentiation

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HIGHLIGHTS

- Modeling biochemical drug effects can suggest candidate combination therapies.
- We begin to apply this strategy to a congenital cause of cognitive disability.
- Dynamics of biochemical pathways underlying synaptic plasticity are simulated.
- Paired parameter changes similar to known drug effects rescue plasticity deficits.
- These simulations suggest possible interventions for Rubinstein–Taybi syndrome.

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ABSTRACT

Congenital cognitive dysfunctions are frequently due to deficits in molecular pathways that underlie the induction or maintenance of synaptic plasticity. For example, Rubinstein–Taybi syndrome (RTS) is due to a mutation in *cbp*, encoding the histone acetyltransferase CREB-binding protein (CBP). CBP is a transcriptional co-activator for CREB, and induction of CREB-dependent transcription plays a key role in long-term memory (LTM). In animal models of RTS, mutations of *cbp* impair LTM and late-phase long-term potentiation (LTP). As a step toward exploring plausible intervention strategies to rescue the deficits in LTP, we extended our previous model of LTP induction to describe histone acetylation and simulated LTP impairment due to *cbp* mutation. Plausible drug effects were simulated by model parameter changes, and many increased LTP. However no parameter variation consistent with a effect of a known drug class fully restored LTP. Thus we examined paired parameter variations consistent with effects of known drugs. A pair that simulated the effects of a phosphodiesterase inhibitor (slowing cAMP degradation) concurrent with a deacetylase inhibitor (prolonging histone acetylation) restored normal LTP. Importantly these paired parameter changes did not alter basal synaptic weight. A pair that simulated the effects of a phosphodiesterase inhibitor and an acetyltransferase activator was similarly effective. For both pairs strong additive synergism was present. The effect of the combination was greater than the summed effect of the separate parameter changes. These results suggest that promoting histone acetylation while simultaneously slowing the degradation of cAMP may constitute a promising strategy for restoring deficits in LTP that may be associated with learning deficits in RTS. More generally these results illustrate how the strategy of combining modeling and empirical studies may provide insights into the design of effective therapies for improving long-term synaptic plasticity and learning associated with cognitive disorders.

1. Introduction

The identification of molecular lesions associated with various neurological disorders that adversely affect cognitive function is providing new opportunities for developing therapeutic interventions. The obvious first choice is to reverse the molecular lesion, or ameliorate its effects, with gene targeting techniques (Corti et al., 2012; Popiel et al., 2012; Rafi et al., 2012). Progress has been made, but this strategy has yet to provide a therapy for a human neurological disorder. A complementary approach is to pharmacologically manipulate an element in the biochemical pathway associated with the molecular lesion to compensate for loss of function (Park et al., 2014; Ehninger and Silva, 2011; Guilding et al., 2007; McBride et al., 2005). A key challenge, however, is to identify the optimal site to target. In

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addition, it is increasingly clear from work in other fields that the targeting of multiple sites simultaneously may yield several advantages over targeting single sites. For example, current pharmacotherapies for cancer and infections often are combination therapies (Bijnsdorp et al., 2011). The majority of these therapies were developed by empirical, trial-and-error methods. However, there is a growing realization that a combination of empirical studies and modeling of intracellular signaling pathways can greatly aid the prediction of effective combinations of drugs (Boran and Iyengar, 2010; Severyn et al., 2011; Zhang et al., 2014). Combination therapies also may offer the advantages of synergism, which can allow lower dosages of the individual drugs to produce a desired effect (Barrera et al., 2005). Dose reductions due to synergism may also minimize undesirable off-target effects of the individual drugs (Zimmermann et al., 2007).

To examine the ways in which computational models and analyses of synergism may help to guide the development of therapies, we modeled aspects of the molecular network that underlies LTP, a neuronal correlate of memory. Several models have been developed to describe the dynamics of intracellular signaling pathways necessary for the induction of LTP (e.g. Bhalla and Iyengar, 1999; Hayer and Bhalla, 2005; Smolen et al., 2006, 2012). These models use empirical estimates of parameters such as cellular enzyme concentrations, Michaelis constants, and binding affinities. The convergence of multiple kinases and their downstream transcription factors to activate gene expression necessary for late LTP and the establishment of LTM is likely to generate regions of synergism in these models. In the present study, we simulated effects of a molecular lesion associated with a cognitive disorder and LTP deficits, and attempted to predict drug combinations that could restore normal LTP and also exhibit synergism.

We selected as an exemplar Rubinstein–Taybi syndrome (RTS), a congenital disorder that is associated with cognitive and learning disability. RTS is associated with mutations in the gene encoding CREB binding protein (CBP), a histone acetyltransferase and an obligatory cofactor in the activation of transcription by cyclic AMP response element binding protein (CREB) (Barco, 2007; Graff and Mansuy, 2009; Park et al., 2014; Petrij et al., 1995; Roelfsema and Peters, 2007) (a small percentage of RTS is due to mutations in a related histone acetyltransferase, p300). In neurons, activation of protein kinase A (PKA) leads to CREB phosphorylation and consequent activation (Matsushita et al., 2001). Some forms of late LTP and LTM require activation of CREB (Kida, 2012; Peters et al., 2009; Pittenger et al., 2002) and co-activation of CBP (Korzus et al., 2004; Levenson et al., 2004). We explored whether our previous model describing LTP induction (Smolen et al., 2006), extended to include CBP and acetylation, could (a) simulate the impaired LTP seen in rodent models for RTS, (b) suggest modulation of specific biochemical parameters as potential targets to rescue the deficit in LTP, (c) identify pairs of parameters that are plausible drug targets and, when concurrently varied, rescue the deficit in LTP, and (d) predict regions of synergism associated with concurrent adjustments to these parameter pairs. For RTS, two synergistic pharmacological manipulations were predicted to rescue LTP.

2. Methods

2.1. The extended model of LTP induction

The model was constructed to simulate induction of late, protein-synthesis dependent LTP at Schaffer collateral synapses in the CA1 region of the hippocampus. An overview of the model, and of stimulus inputs, follows. Ordinary differential equations describe the dynamics of kinase activities, gene expression, and synaptic weight. As schematized in Fig. 1, stimuli activate three signaling pathways. Increased [Ca^{2+}] activates CaM kinase II (CaMKII), Ras activation leads to

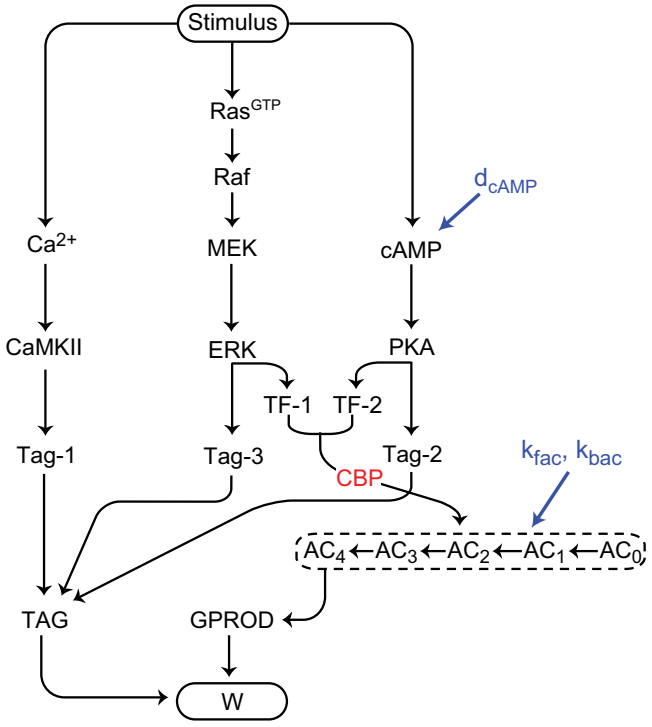

Fig. 1. Model of key postsynaptic signaling pathways that underlie the induction of late LTP and of the mutation linked to RTS. Blue arrows indicate the sites of action of the key parameters used to model drug effects – k_{fac} for acetyltransferase activators, k_{bac} for deacetylase inhibitors, and d_{cAMP} for PDE inhibitors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

activation of the ERK isoforms of MAPK, and increased [cAMP] activates PKA. These pathways are established as essential for LTP. PKA phosphorylation of an unspecified substrate is necessary to set a synaptic tag required for synaptic "capture" of proteins necessary for late LTP (Barco et al., 2002; Frey and Morris, 1997; Redondo and Morris, 2011). This PKA-sensitive synaptic tag is denoted Tag-2 (Fig. 1). Phosphorylation of another substrate Tag-1 by CaMKII is also necessary to set the tag (Fig. 1) as data suggests (Chen et al., 2001). Inhibition of ERK blocks LTP (English and Sweatt, 1997; Rosenblum et al., 2002), thus ERK phosphorylates another tag substrate, Tag-3. The value of a tag variable is set proportional to the product of the levels of Tag-1–Tag-3. ERK is known to phosphorylate transcription factors (TFs), inducing genes important for LTP (Impey et al., 1998; Waltereit et al., 2001). In the model activated ERK phosphorylates a TF denoted TF-1. Activation of CREB is essential for at least some forms of late LTP. Inhibiting PKA attenuates CREB phosphorylation and LTP. Thus a second TF, TF-2, represents CREB and is phosphorylated by PKA.

We model histone acetylation, as necessary for expression of a representative gene product necessary for LTP, denoted GPROD. Acetylation is included because the essential CREB cofactor CBP drives acetylation and gene induction and is deficient in RTS. In the model four acetylations are needed to induce GPROD synthesis. Both TF-1 and TF-2 need to be phosphorylated to induce these acetylations. The state with four acetylations is denoted AC4 (Fig. 1). The rate of GPROD expression is proportional to the amount of AC4. LTP is, then, modeled as an increase in a synaptic weight W. The rate of increase is simply taken as proportional to the product of the tag variable with GPROD.

In simulations LTP was induced by spaced tetani. Stimulus inputs were not modeled as differential equations, but rather as square-wave increases in synaptic Ca^{2+}, [cAMP], and Ras activity. Four 1-s tetani at intervals of 5 min were simulated. This protocol was previously used with an RTS mouse model (Alarcon et al.,