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The role of tonic and phasic dopamine for long-term synaptic plasticity in the prefrontal cortex: A computational model

Denis Sheynikhovich [a,*], Satoru Otani [b], Angelo Arleo [a]

[a] Laboratory of Neurobiology of Adaptive Processes, CNRS-UMR7102, UPMC-Paris 6, 9 Quai St. Bernard, F-75005 Paris, France
[b] Laboratory of Psychopathology of Central Nervous System Diseases, INSERM-U952, CNRS-UMR7224, Univ. Paris 6, 9 Quai St. Bernard, F-75005 Paris, France

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ABSTRACT

This work presents a computational model of dopamine (DA) influence on long-term potentiation (LTP) and long-term depression (LTD) in the prefrontal cortex. Distinct properties of the model are a DA-concentration-dependent switch from depression to potentiation during induction of plasticity, and an inverted-U-shaped dependence of protein synthesis on the level of background DA. Protein synthesis is responsible for the maintenance of LTP/LTD in the model. Our simulations suggest that *in vitro* experimental data on prefrontal plasticity, induced by high-frequency stimulation, may be accounted for by a single synaptic mechanism that is slowly (on the timescale of minutes) activated in the presence of DA in a concentration-dependent manner. The activation value determines the direction of plasticity during induction, while it also modulates the magnitude of plasticity during maintenance. More generally, our results support the hypothesis that phasic release of endogenous DA is necessary for the maintenance of long-term changes in synaptic efficacy, while the concentration of tonic DA determines the direction and magnitude of these changes in the PFC.

1. Introduction

The prefrontal cortex (PFC) is thought to mediate executive functions, including strategic organization of behavior (Fuster, 1995). These functions were shown to rely on (short-term) working memory, thought to be represented by persistent activity within the PFC (Goldman-Rakic, 1995), as well as on long-term memory, represented by persistent synaptic changes (Fuster, 1995; Touzani et al., 2007). Both of these memory representations were shown to be strongly modulated by dopamine (DA) (Seamans and Yang, 2004; Kolomiets et al., 2009). In particular, for both memory types (i) the role of tonic (background) DA levels is different from that of phasic (or event-related) DA release (Grace, 1991; Seamans and Yang, 2004; Kolomiets et al., 2009); and (ii) optimal DA levels are required for best performance. The latter property is expressed by an inverted-U-shaped dependence of task performance (working memory) or magnitude of synaptic changes (long-term memory) on DA levels (Jay, 2003; Seamans and Yang, 2004; Goto et al., 2007; Kolomiets et al., 2009).

Whereas a fair amount of theoretical work has been devoted to DA modulation of persistent activity and working memory (Durstewitz et al., 2000b; Cohen et al., 2002; Rolls et al., 2008), no theoretical models, to our knowledge, addressed the role of DA for long-term plasticity in the PFC. The present work attempts to fill this gap by proposing a model of DA modulation of long-term plasticity in the PFC. In particular, we focus on a series of studies that investigated DA influence on long-term depression (LTD) and long-term potentiation (LTP) induced by high frequency stimulation (HFS, 50 Hz) in the rat PFC *in vitro* (Otani et al., 1998, 1999; Matsuda et al., 2006; Kolomiets et al., 2009). In line with general properties of DA in the PFC outlined above, three main conclusions can be made from the results of these studies. First, a phasic DA release during synaptic stimulation is required to trigger plasticity at this frequency (Otani et al., 1998, 1999). Second, tonic DA levels modulate the *direction* of plastic changes in the PFC, since the same HFS results in either LTD or LTP depending on DA conditions in prefrontal slices 10–40 min before the stimulation. Namely, insufficient time of DA exposure results in no plasticity or LTD (for concentrations in the range 3–100 μM), whereas prolonged bath at a low tonic DA (1–10 μM) results in LTP (Fig. 1A, Matsuda et al., 2006; Kolomiets et al., 2009). Third, tonic DA modulates the *amplitude* of plastic changes in the PFC. In the LTP regime, different tonic DA concentrations result in LTP of different magnitude such that the dependence of the LTP strength on DA concentration follows an inverted-U-shaped curve (Fig. 1B, Kolomiets et al., 2009; Xu et al., 2009; Jay, 2003). This is in contrast to the hippocampus where DA influence is limited to the maintenance phase of long-term plasticity (via

* Corresponding author. Tel.: +33 144272133; fax: +33 144272669.
E-mail addresses: denis.sheynikhovich@upmc.fr (D. Sheynikhovich), satoru.otani@snv.jussieu.fr (S. Otani), angelo.arleo@upmc.fr (A. Arleo).
URL: http://www.anc.upmc.fr/dsheynikhovich.html (D. Sheynikhovich).

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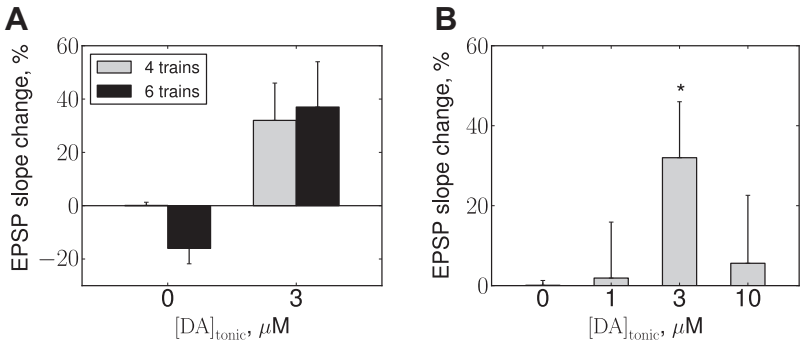

Fig. 1. Experimental evidence for DA-dependent switch from LTD to LTP (A) and an inverted-U-shaped dependence of LTP amplitude on tonic DA concentration (B). (A) A high-frequency stimulation (50 Hz) resulted in no-change (when 4 trains were delivered) or LTD (when six trains were delivered) in vitro, when no tonic DA was present in the bath (0 tonic DA condition). In contrast, when DA concentration was set to 3 μM, the same stimulation resulted in LTP, when applied after 40 min DA bath (3 μM tonic DA condition). (B) Bars denote the amplitude of LTP, induced by the HFS at different concentrations of tonic DA in the bath. At 3 μM LTP amplitude was significantly different compared to non-DA condition ('*' denotes $p < 0.01$). The amplitude of plasticity was measured by the initial rising slope of excitatory post-synaptic potential (i.e. 1 ms from the onset) ±SE. Adapted from Kolomiets et al. (2009) with permission.

cAMP-dependent pathways, Frey and Morris, 1998 and Navakkode et al., 2004, 2007 suggesting) that direction of plasticity (which is determined during induction) is DA-independent.

In this modeling study we sought to understand how known properties of tonic and phasic DA modulation in the PFC can lead to observed changes in direction and magnitude of long-term plasticity. In our model, the direction of plasticity is determined by DA influence during plasticity induction while the plasticity amplitude is determined by DA influence during maintenance phase of LTP. Our simulations suggest that DA actions during both phases can be accounted for by considering DA-dependent activation of a single synaptic mechanism.

2. Model of synaptic plasticity under DA influence

In our model of long-term plasticity an artificial neuron is first exposed to a 'bath period' with different DA conditions and then stimulated by high-frequency synaptic input. As a result of stimulation, synapses of the neuron can undergo plastic changes that occur in two phases, plasticity induction and plasticity maintenance, as described below. The evolution of the average synaptic strength is monitored after the stimulation to see whether long-term synaptic changes were induced.

All simulations were performed using NEURON software (version 7.1, Carnevale and Hines, 2006).

2.1. Neuron model

We used a two-compartment model neuron with compartment sizes and passive parameters taken from the study of Durstewitz and Seamans (2002). A two-compartment neuron model was chosen to reflect spatial structure of layer V PFC pyramidal neurons that have long apical dendrites (>500 μm, Seamans et al., 1997) extending to layers I–II where electrical stimulation was applied in the experimental studies (Otani et al., 1998; Kolomiets et al., 2009). Ionic conductances, Ca^{2+} and K^+ dynamics were modeled identically to the same study, except that slow potassium current I_{Kslow} with conductance 1.0 mS/cm^2 was added which was modeled as in Schreiber et al. (2004). The model neuron had $N = 100$ synapses with a plastic AMPA and non-plastic NMDA conductance each. Synaptic currents were modeled by double exponential functions with maximal AMPA and NMDA synaptic conductances $g_{AMPA,max} = 4$ nS ($g_{NMDA,max} = g_{AMPA,max}/50$) and short-term depression with utilization parameter $U_{SE} = 0.6$ and recovery time constant $t_{rec} = 800$ ms (Tsodyks and Markram, 1997; Durstewitz and Gabriel, 2007). To model plasticity, synaptic conductances were scaled by efficacies w_n ($n = 1, \ldots, N$) that were initialized at $w_n(0) = \hat{w} = 1$ and remained fixed for NMDA conductances, while for the AMPA conductances they were updated according to the synaptic plasticity rules described in the following sections.

The conductance of the slow potassium current g_{Kslow} and peak synaptic conductances ($g_{AMPA,max}$, $g_{NMDA,max}$) were tuned to reproduce voltage responses of PFC neurons to step currents and HFS recorded *in vitro* (neuron recording data provided by Otani, see also Kolomiets et al., 2009), see Section 3.

2.2. DA influence during a 'bath period'

A principal feature of the DA-dependent switch from LTD to LTP is that the same high frequency stimulation results in either potentiation or depression, depending on the DA conditions in the slice during 10–40 min time period before the stimulation (Fig. 1A, Matsuda et al., 2006; Kolomiets et al., 2009). This suggests that the direction of synaptic changes, at least in the PFC, depends not only on how the synapse is stimulated but also on a long-term (i.e. on the time scale of tens of minutes) history of the synapse before the stimulation.

On the basis of these data, we propose that the presence of DA in the bath slowly (i.e. at the time scale of tens of minutes) activates an identified intracellular process, such that its level of activation at the time of the stimulus arrival determines the direction of plasticity. For clarity, we describe this process in terms of an activation of a putative DA-dependent kinase (DAK, see Fig. 2A), although in reality it may correspond to a combined action of multiple kinases and/or phosphatases (such as those implicated in DA-activated cascade including adenylyl cyclase 5 (AC5), cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), protein phosphatase 2A (PP2A) and dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32)). Detailed models of this signaling pathway in striatal neurons (Lindskog et al., 2006; Nakano et al., 2010) suggest the importance of a positive feedback loop between DA-dependent activation of PKA, PP2A and DARPP32. This is taken into account in our model by describing the activation of DAK by an autocatalytic process:

$$\frac{d[\mathrm{DAK}]}{dt} = -a \cdot [\mathrm{DAK}]^2 + b \cdot \beta([\mathrm{DA}]_{\mathrm{to}}) \cdot [\mathrm{DAK}] \qquad (1)$$

with rate coefficients $a = b = 0.0033$ s^{-1}. The $[\mathrm{DA}]_{\mathrm{to}}$ denotes tonic DA concentration in the slice (set to either 0, 1, 3, or 10 μM in the simulations below). The experimentally observed dependence of the amplitude of plasticity on DA concentration in the slice is taken

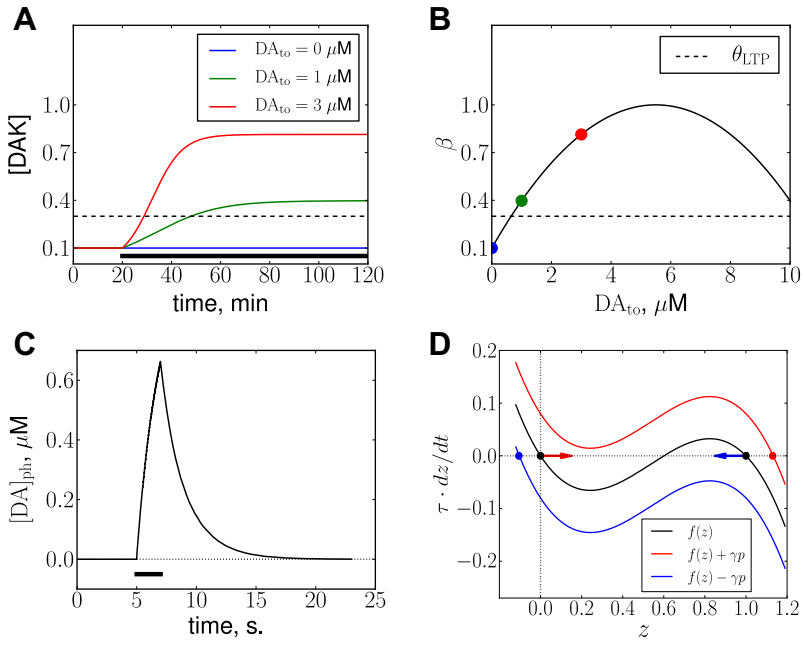

Fig. 2. Overview of the main components of the model. (A) Evolution of [DAK] at bath DA concentrations $[DA]_{to} = 0$ μM (blue line), $[DA]_{to} = 1$ μM (green line) and $[DA]_{to} = 3$ μM (red line). The thick black line denotes the period of the DA bath. The dashed line denotes the threshold for LTP (θ_{LTP}). (B) Function $\beta([DA]_{to})$ describes the modulation of the rate of [DAK] activation by tonic DA (see Eq. (2)). Colored dots mark the value of β for tonic DA concentrations equal to 0, 1, and 3 μM. (C) Phasic DA release in μM induced by 2 s 50 Hz stimulation. Black bar denotes stimulation time. (D) Dynamics of the z variables. In the absence of stimulation the fixed points of the synaptic state are $z = 0$ (depression) and $z = 1$ (potentiation), marked by the black dots. If the synapse is tagged for LTP ($h_n = 1$) and $p > 0$, z can pass from depression for potentiation (corresponding to the movement of the phase point from the left black dot towards the red dot). For the LTD tag ($h_l = 1$), a synapse potentiated earlier can pass to the depressed state (corresponding to the movement of the phase point from the right black dot towards the blue dot).

into account in the term $\beta([DA])$ which modulates the forward reaction rate (Fig. 2C):

$$\beta([DA]_{to}) = -\frac{1}{s^2} \cdot ([DA]_{to} - \mu)^2 + 1 \quad (2)$$

where $\mu = 5.5$ μM determines the concentration of tonic DA at which the rate of DAK activation is fastest and $s = 5.8$ μM sets the range of concentrations at which plasticity can be induced. We chose a simple quadratic dependence on the basis of experimental data from Kolomiets et al. (2009), but the exact shape of the dependence is not essential as long as the value of β (i) is non-zero at $[DA]_{to} = 0$; (ii) has its maximum between 1 and 10 μM (Kolomiets et al., 2009). Eqs. (1) and (2) ensure that the level of DAK activation changes in the range $[1 - \mu^2/s^2, 1]$ depending on DA concentration in the slice.

In order to account for the time dependence of the DA influence, we assume that the activation level of the DAK above threshold $\theta_{LTP} = 0.3$ (denoted by the dashed line in Fig. 2A and B) at the time of stimulation is a necessary condition for LTP induction. If the activation level is lower than θ_{LTP}, as a result of, e.g., insufficient time of DA exposure or unfavorable DA conditions, only LTD can be induced (see the next section).

2.3. DA influence during induction

According to the theory of synaptic tagging and capture (Frey and Morris, 1997; Frey and Morris, 1998), synaptic stimulation results in setting of 'tags' (thought to be implemented by an activated form of a particular kinase such as, e.g., CaMKII for LTP, Reymann and Frey, 2007) at some synapses. Tagged synapses are potentiated (if the LTP tag is set) or depressed (if the LTD tag is set) for a period of time <40 min, corresponding to an early phase of LTP or LTD. In order to maintain these changes for a longer period of time, protein synthesis is required (see Section 2.4).

Similarly to Clopath et al. (2008) (see also Abarbanel et al., 2005) we model synaptic tags by binary variables l_n and h_n corresponding to LTD and LTP tags, respectively, at each synapse n. Only one of the tags can be equal to 1 at any time and the non-tagged state corresponds to $h_n = 0$, $l_n = 0$. The probability of setting a tag, i.e. *plasticity rate*, is given by:

$$\rho = A \cdot g_{syn} \cdot [V - \theta_V]^+ \quad (3)$$

where g_{syn} is the total synaptic conductance, V is membrane voltage at the synapse and $[\cdot]^+$ denotes rectification, i.e. $[x]^+ = x$ if $x > 0$ and zero otherwise. The constant parameter $A > 0$ was tuned such that in the simulations below $\sum_n (h_n + l_n) \leqslant N$ (i.e. it was fixed with respect to the simulation time step and kept the same for all simulations). The rise in synaptic conductance g_{syn} serves as a presynaptic spike detector. According to Eq. (3), a synapse can become tagged only if the neuron is depolarized as a consequence of the synaptic input above the threshold value $\theta_V = -50$ mV. A tag represents only a temporary change at the synapse and so a tagged synapse will return to an initial state with stochastic rates $k_L = 0.033$ min^{-1} (for an LTD tag) and $k_H = 0.083$ min^{-1} (for LTP an tag), unless it is consolidated.

The plasticity rate ρ (Eq. (3)) determines when a tag is set, but it does not determine the type of tag. In the present model, the tag will be either LTD or LTP depending on the value of [DAK] at the time of the stimulation (Eq. (1)). Thus, a synapse that has no tags set, can change its state under the following conditions:

- if $0 < [DAK] \leqslant \theta_{LTP}$, the synapse switches to the state $l_n = 1$, $h_n = 0$ (i.e. LTD tag is set) with probability ρ_{LTD} given by Eq. (3) with $A = A_{LTD} = 4 \times 10^{-4}$ nA^{-1}
- if $[DAK] > \theta_{LTP}$, the synapse switches to the state $l_n = 0$, $h_n = 1$ (i.e. LTP tag is set) with probability ρ_{LTP} given by Eq. (3) with $A = A_{LTP} = 10^{-4}$ nA^{-1}
- otherwise, the synapse remains in the non-tagged state $l_n = 0$, $h_n = 0$.

2.4. DA influence during maintenance

As a result of stimulation, plastic changes can be induced at some synapses with corresponding transient increase (early-LTP) or decrease (early-LTD) in their strength. These transient changes may become persistent if plasticity related proteins (PRPs) are synthesized and reach the tagged synapse (Frey and Morris, 1997). Protein synthesis is under control of DA (Navakkode et al., 2007).

DA signaling in the PFC occurs in two distinct modes (Grace, 1991; Goto et al., 2007). Tonic, or background, DA signal provides a constant low concentration of DA that is simulated in slice experiments by low-concentration DA bath. This signal is thought to be provided by the background population activity of dopaminergic neurons in the VTA (Goto et al., 2007; Floresco et al., 2003). Phasic, or event-related, release of DA occurs as a result of burst firing of DA neurons in response to salient environmental stimuli. In slices, high-frequency stimulation results in DA release from dopaminergic axon terminals present in the slice that can be considered as an *in vitro* model of the event-related DA release (Young and Yang, 2005; Kolomiets et al., 2009). It has been suggested that DA action in the PFC is determined by the relative values of tonic vs phasic DA levels (Grace, 1991; Kolomiets et al., 2009).

While tonic DA signal in our model exerts its influence via the DA-dependent activation of DAK as described in the previous section, the phasic DA signal is modeled according to the study of DA release kinetics in the prefrontal cortex (Garris and Wightman, 1994). In their model, each stimulation pulse releases a fixed quantity of DA (denoted as $[DA]_p = 10.7$ nM) into extracellular fluid, while DA uptake is governed by a first-order process with rate $k = 0.53\ s^{-1}$:

$$\frac{d[DA]_{ph}}{dt} = -k \cdot [DA]_{ph} \tag{4}$$

A 2 s train of 50 Hz stimulation results in phasic DA release with the amplitude of about 6.5 μM and decay period of ≈5 s (Fig. 2C).

Protein synthesis is controlled by both phasic and tonic DA levels and is described by a first-order process:

$$\frac{dp}{dt} = k_f \cdot [DA]_{ph} \cdot [DAK] \cdot (1 - p) - k_b \cdot p \tag{5}$$

where p denotes the concentration of synthesized proteins (in dimensionless units with the maximal value of 1), $k_f = 0.17$ mM/s and $k_b = 2.8 \times 10^{-4}\ s^{-1}$ are the forward and backward rate coefficients. According to Eq. (5) the concentration of PRPs starts to grow upon stimulation-induced phasic DA release, and the growth rate is proportional to the concentration of active DAK. The latter is determined by the background DA concentration (see Eqs. (1) and (2)).

Finally, the protein-synthesis-dependent consolidation of a synapse is modeled by a bistable process, similar to that proposed by Lisman (1985) (see also Lisman, 1989; Pi and Lisman, 2008; Clopath et al., 2008). More specifically, the consolidated state of synapse n is described by variable z_n governed by the following differential equation:

$$\tau_z \frac{dz_n}{dt} = f(z_n) + \gamma(h_n - l_n)p \tag{6}$$

where $f(z_n) = z_n(1 - z_n)(z_n - 0.6)$ is shown in Fig. 2D (black line), $\tau_z = 2$ min and $\gamma = 0.35$. In the absence of plasticity related proteins (i.e. $p = 0$) or if no tags are set at the synapses (i.e. $h_n = 0$ and $l_n = 0$), Eq. (6) describes bistable dynamics with two stable states $z_n = 0$ and $z_n = 1$ (denoted by black dots in Fig. 2D), that represent persistently depressed or persistently potentiated state of the synapse, respectively. When a tag is set at the synapse *and* the concentration of PRPs is sufficiently high, z_n can pass from depression to potentiation (i.e. if $h_n = 1$ and $l_n = 0$, along the red arrow in Fig. 2D), or from potentiation to depression (if $h_n = 0$ and $l_n = 1$, along the blue arrow in Fig. 2D). When one of the stable states is reached, it is kept indefinitely long, unless a new stimulation induces a switch between states. Initially, 1/3 of the synapses are in a persistently potentiated state (i.e. $z_n = 1$) ensuring the capacity of the neuron to express late LTD (O'Connor et al., 2005). A potential biological candidate for z_n is protein kinase Mζ, necessary for late phase LTP (Sajikumar et al., 2005).

The synaptic weight change as a result of stimulation has contributions both from induction and maintenance phases:

$$\Delta w_n = \hat{w} \cdot (h_n - 0.5 \cdot l_n + 2 \cdot z_n) \tag{7}$$

where $\hat{w}$ is the weight value before stimulation. According to Eq. (7), plasticity induction phase results in a transient weight change when $h_n = 1$ or $l_n = 1$ (corresponding to early LTP or early LTD, respectively), since synaptic tags decay to zero with time. Efficacy of transient depression is twice smaller than that of potentiation in order to reflect experimental evidence from minimal experiments in hippocampal slices (O'Connor et al., 2005). The long-term change in the synaptic efficacy is encoded by the changes in the z_n variable, resulting from the coincident setting of synaptic tags and protein synthesis (Frey and Morris, 1998; Clopath et al., 2008). In Figs. 4–6, the average change in synaptic weight is measured as $\langle w/w(0)\rangle$ where $\langle w\rangle = N^{-1} \cdot \sum_n (\hat{w} + \Delta w_n)$ (see Eq. (7)).

3. Results

Influence of DA on long-term plasticity was investigated by stimulating the artificial neuron with HFS (3 or 6 trains of 100 pulses at 50 Hz) under various DA conditions and monitoring the evolution of the average synaptic strength for several hours after the stimulation. Below we show that the simulated neuron behaves similarly to real PFC neurons in relevant stimulation regimes and that DA-modulation of plasticity in these neurons reproduces neurophysiological data (Matsuda et al., 2006; Kolomiets et al., 2009).

3.1. Reproduction of voltage response of PFC neurons

Most of the neurons recorded in the studies by Kolomiets et al. (2009) and Matsuda et al. (2006) were regularly spiking and their response to the HFS exhibited strong adaptation (an example of the response of one such neuron to a step current and HFS is shown in Fig. 3, top row). Since we were interested in reproducing DA effects on *PFC* neurons, we first ensured that the neuron model we use is capable of reproducing responses of real PFC neurons to step currents and HFS. Spiking frequency in response to step currents was tuned by adjusting the conductance of the slow potassium current (Schreiber et al., 2004) (see Fig. 3A, bottom row). Fast adaptation during HFS in the model is due to short term depression (Tsodyks and Markram, 1997) (see Fig. 3B, lower panel).

3.2. Synaptic plasticity in the absence of tonic DA

We then tested whether long-term synaptic plasticity can be induced by HFS in the absence of tonic DA. Weak stimulation (3 trains of 100 pulses at 50 Hz) did not result in a significant change of synaptic strength one hour after the stimulation (Fig. 4A, top) whereas a longer stimulus (6 trains at the same frequency) resulted in long-term LTD (Fig. 4B, top).

In the absence of tonic DA, activation of DAK is lower than the threshold for LTP (see Fig. 2A) and hence only LTD can be induced in the model by the HFS in these conditions. Initial strong depression of synaptic weights shortly after stimulation is due to the contribution from synaptic tags (shown by blue lines in

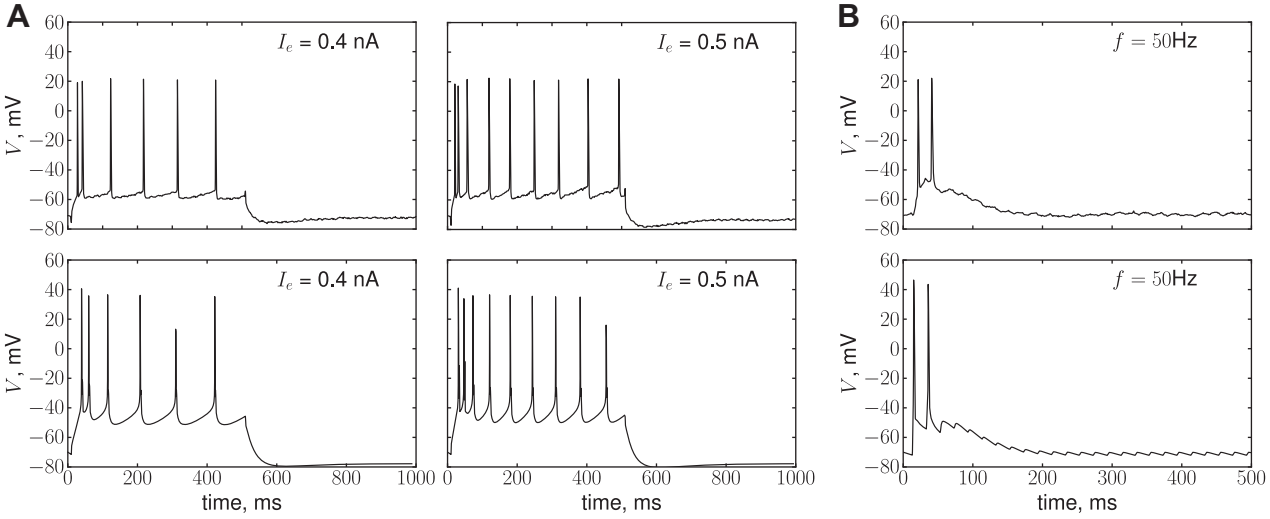

Fig. 3. Voltage responses of real (top row, data provided by S. Otani) and simulated (bottom row) PFC neurons to injected step currents (A) and HFS at 50 Hz (B). (A) Current amplitudes 0.4 nA (left column) and 0.5 nA (right column), duration 500 ms. (B) First 500 ms of the response to the HFS.

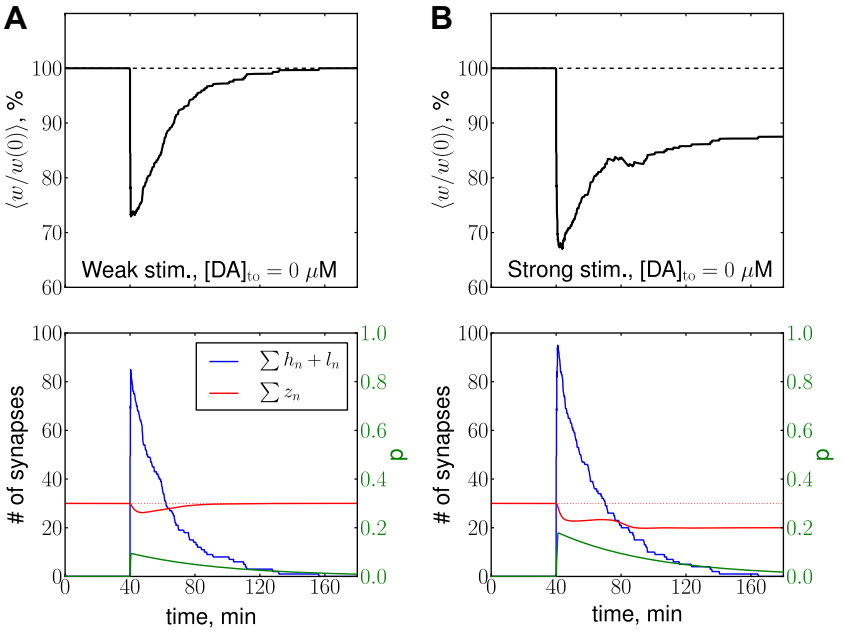

Fig. 4. Synaptic plasticity in the absence of tonic DA as a result of stimulation by weak HFS (3 trains at 50 Hz, A) or strong HFS (6 trains at 50 Hz, B) applied at t = 40 min. Top row: Evolution with time of the average weight change $\langle w/w(0)\rangle$ (see Section 2.4) of one simulated neuron. Bottom row: Evolution of synaptic tags (blue line), consolidation variables (red line) and the concentration of synthesized PRP (green line) in the model. Only persistently potentiated synapses can undergo LTD in the model. Hence, we assume that $\sum_n z_n = 30$ before the stimulation started (see Section 2.4).

Fig. 4, see also Eq. (7)). This depression is transient, since synaptic tags decay to zero within 1–1.5 h after stimulation.

Protein synthesis is necessary in order to consolidate tagged synapses in the depressed state. The concentration p of synthesized PRPs (shown by green lines in Fig. 4) grows as a result of phasic DA input, which is larger in the case of stronger stimulation. Synaptic weights at the late phase of plasticity are controlled by consolidation variables z_n (shown by red lines in Fig. 4). Initially, 30% of synapses are potentiated so that $\sum_n z_n(0) = 30$. When the concentration of PRP rises, tagged synapses can pass from the persistently potentiated ($z_n = 1$) to the persistently depressed ($z_n = 0$) state, resulting in a smaller number of persistently potentiated synapses, i.e. in late Ltd.

In Fig. 4B, a stronger stimulation resulted in a higher number of tagged synapses as well as in a higher phasic DA input, both contributing to the number of synapses that expressed late LTD, and hence to a persistently decreased average synaptic weight of the neuron. Since the direction of plasticity is determined by the DAK concentration at the time of induction, LTD will also be induced in our model after a short term application of non-zero DA concentrations (i.e. before the [DAK] crosses the dashed line in Fig. 2A), consistently with experimental data (Law-Tho et al., 1994; Otani et al., 1998).

3.3. Synaptic plasticity in the presence of tonic DA

Next, we studied how the sign and magnitude of plasticity changes in our model depending on different tonic DA conditions. DA bath was simulated by setting $[DA]_{to}$ to 1, 3, or 10 μM at time t = 0. At t = 40 min the same 50 Hz HFS stimulation as before was

delivered and the change in synaptic efficacy was measured according to Eq. (7) for two hours after stimulation. The only way tonic DA concentration influences plasticity in our model is through the activation of DAK. Hence, DA bath at different concentrations corresponds in our model to different values of [DAK] at the time of the stimulation (see Fig. 2A and B).

The same HFS that resulted in LTD in the absence of tonic DA, led to strong LTP after 40 min application of 3 μM DA (Fig. 5A, top), while the magnitude of LTP decreased at 1 μM (Fig. 5B, top) and 10 μM (identical, not shown) reproducing the data reported in Kolomiets et al. (2009). The mechanism of modulation of the LTP amplitude is similar to that for LTD (see previous section), with two main differences. First, for DA concentrations explored here, the DAK activation reached the threshold for LTP, such that the plasticity direction switched from depression to potentiation. Second, the rise in DAK concentration due to the presence of tonic DA led to a faster protein synthesis (Eq. (5), green lines in Fig. 5, bottom row), resulting in different LTP amplitudes for different concentrations of tonic DA.

In summary, our model reproduces the main features of DA modulation of long-term synaptic plasticity observed *in vitro* (Fig. 1, Kolomiets et al., 2009; Matsuda et al., 2006). First, the model exhibits DA-dependent switch from LTD to LTP under the *same* HFS (Fig. 6A). Second, in the LTP regime, the magnitude of LTP follows an inverted-U-shaped dependence on the concentration of tonic DA (Fig. 6B). Both of these effects are due to the assumption that extracellular tonic DA activates an intracellular process (e.g., a protein cascade) in a DA-concentration-dependent manner. The level of activation determines directly whether depression or potentiation can be induced (during plasticity induction phase). In addition, it indirectly determines the magnitude of plasticity by influencing the rate of PRP synthesis. A phasic release of DA is necessary for the late phase of LTP, as was observed in prefrontal slices (Huang et al., 2004).

4. Discussion

In this work we proposed a mechanism of DA influence on long-term plasticity within the PFC, induced by HFS. In this mechanism, the sign of plasticity is determined by background DA conditions, whereas the magnitude of plasticity depends on the relative levels of phasic DA release and tonic DA concentration. Moreover, the model makes a specific prediction about the existence of a single DA-dependent mechanism that influences plasticity during both induction and maintenance phases.

In a 'standard model' of synaptic plasticity, the sign of plasticity is thought to be determined by a rise of calcium concentration at the synapse, resulting from synaptic stimulation (Lisman, 1985; Shouval et al., 2002). The calcium rise is a detector of coincidence between pre-synaptic stimulation and post-synaptic activity. More recent models suggest that the sign of plasticity may depend on more than one coincidence detector, acting on time scales of up to 1 s (Karmarkar and Buonomano, 2002; Pfister and Gerstner, 2006). In contrast, experimental data on prefrontal long-term plasticity (Matsuda et al., 2006; Kolomiets et al., 2009) suggest that DA conditions in the slice 20–40 min before the stimulation determine the direction of synaptic changes. Thus, dopamine modulation, at least in the PFC, is a determinant of the sign of long-term synaptic changes which can act in addition to coincidence detectors at the synapse. Here we propose that when present in the slice, DA slowly activates a synaptic mechanism, possibly a protein cascade, that determines the sign of synaptic changes. In order to highlight the role of DA in determining plasticity sign, we used a simplified learning rule that coupled pre-synaptic and post-synaptic activity without attempting to model more complex plasticity phenomena (see Shouval et al., 2002; Clopath et al., 2008 for more realistic learning rules).

There are a number of potential candidates for the putative DA-activated mechanism in the PFC neurons. First, experimental results by Otani et al. (1999) and Kolomiets et al. (2009) suggest an implication of extracellular signal-regulated kinases (ERK1/2, also known as MAPK) in both prefrontal LTD and LTP. Namely, the application of a specific ERK inhibitor PD98059 blocked both the LTD (induced by 50 Hz HFS after 15 min application of 100 μM DA, (Otani et al., 1999)) and LTP (induced by the same HFS after 40-min bath with 3 μM DA, (Kolomiets et al., 2009)). Moreover, in the LTP experiments, western blot analysis has shown a significant enhancement of ERK1/2 phosphporylation after 3 μM DA bath, but not after 1 and 10 μM bath (in which LTP amplitude was absent). However, in both the LTD and LTP (i.e. at 3 μM) conditions the phosphorylation levels of ERK1/2 were similar, suggesting that the sign of plasticity is not determined by ERK activity in a way predicted by our model. Second, assuming that ERK activation is necessary to produce

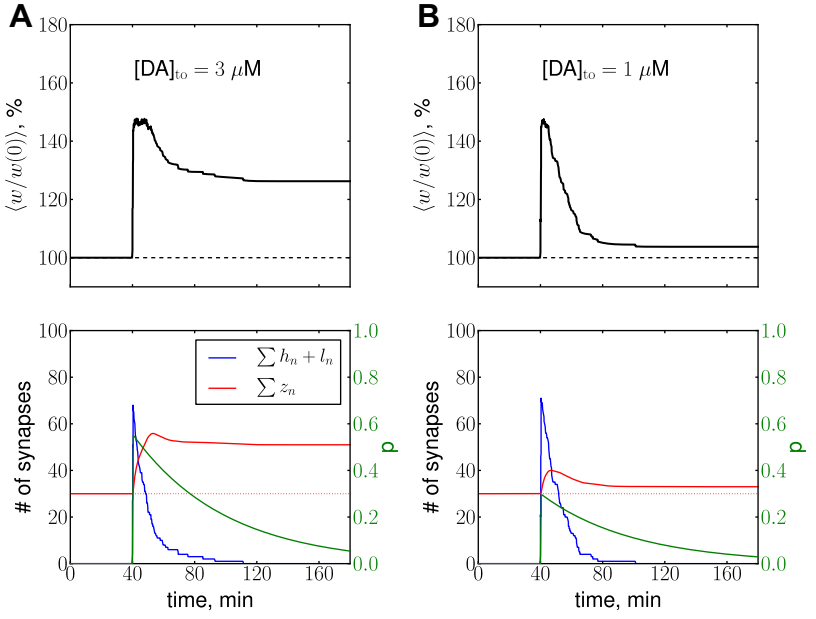

Fig. 5. Synaptic plasticity after DA bath at concentrations 3 μM (A) and 1 μM (B). Weak HFS (3 trains at 50 Hz) was applied at $t = 40$ min. See caption of Fig. 4 for details.

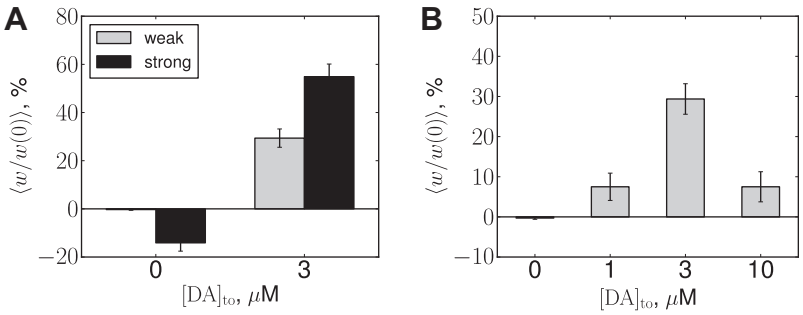

Fig. 6. A summary of simulated DA influence on long-term plasticity in the simulated PFC neurons. The bars correspond to the magnitude of plasticity (average weight change over 10 neurons in % relative to baseline ±STD) 120 min after the HFS application at different tonic DA concentrations. A. DA-dependent switch from LTD to LTP when tonic DA concentration changes from 0 to 3 μM. B. The LTP magnitude follows an inverted-U-shaped dependence from tonic DA concentration.

LTP and LTD, it is possible that protein kinases upstream from ERK could mediate DA-dependent plasticity changes. A potential candidate for DA-activated kinase is protein kinase C (PKC), acting upstream of ERK and implicated in both LTP and LTD in the hippocampus (Malenka and Bear, 2004). Recently, it has been shown that D1 receptor can be coupled to phospholipase C and activate PKC (see Seamans and Yang, 2004 for a review). Interestingly, both LTP and LTD in the PFC depend on the activation of metabotropic glutamate receptors, activation of which is also linked to phospholipase C and PKC (Otani et al., 2002).

A third potential candidate is PKA. Dopamine activates intracellular cascades via its action on five DA receptors divided into two receptor families. The D1-receptor family (D1 and D5) and D2-receptor family (D2–D4) are positively and negatively coupled to the production of cAMP, respectively (but see Floresco et al., 2006 for the evidence of specific function of D4 receptors in the PFC). Elevation of cAMP activates PKA, phosphorylation and dephosphorylation of which were shown to correlate with LTP and LTD, respectively, in the hippocampus (Malenka and Bear, 2004). In the PFC, PKA levels were shown to increase during LTP induction (Jay et al., 1998), LTP in DA transporter knock-out mice and LTD in rats were prevented by PKA inhibitors (Xu et al., 2009; Otani et al., 2002). In an ongoing modeling study we are testing a hypothesis that DA via D1 and D2 receptor family change PKA activation levels by opposite modulation of cAMP production. A decrease in PKA activity will lead to LTD, while increased PKA activation will inhibit protein phosphatase 1 (PP1) and thereby disinhibit CaMKII phosphorylation and lead to LTP (Malenka and Bear, 2004; Graupner and Brunel, 2010).

There is a general agreement in the literature about the distinction between tonic and phasic DA signalling in the PFC (Lavin et al., 2005; Seamans and Yang, 2004). This distinction is based on studies examining midbrain DA neurons activity (Grace, 1991; Floresco et al., 2003), microdialysis measurements of extracellular DA concentration in the PFC (Hedou et al., 2001), and voltammetric measurements of phasic DA release following stimulation of DA neurons (Garris and Wightman, 1994). However, how these differential signals are detected by prefrontal neurons is not clear. In our model, tonic DA concentration and phasic DA release are described by separate variables. There are three possible ways of how the two signals can be distinguished by prefrontal neurons. First, this distinction can be based on separation of time scales. Indeed, changes in tonic DA concentration occurs on time scale of tens of minutes, or DA levels can be persistently elevated (e.g., after chronic stress) or decreased (e.g. in DAT-knockout mice) conditions. In contrast, phasic DA release occurs on the time scale of seconds. Separate synaptic processes can be sensitive to fast and slow changes in DA concentration, enabling separation of the tonic and phasic DA signals. Second, it is possible that the two signaling modes are distinguished due to different affinities of DA receptors. Tonic DA level may be sufficient to strongly activate high-affinity D2 receptors, but weakly activate low-affinity D1 receptors. Phasic bursts will then preferentially activate D1 receptors (Dreyer et al., 2010). Third, differential localization of D2/D1 receptor types can give rise to the separation of signaling modes. One hypothesis suggests that synaptically located D2 receptors will be preferentially activated by phasic bursts, while tonic DA signal may reach extrasynaptically located D1 receptors (Seamans and Yang, 2004).

A large body of experimental and theoretical studies address the role of DA for (short-term) working memory (see Seamans and Yang, 2004 for a review of experimental data and Durstewitz et al., 2000b; Cohen et al., 2002; Rolls et al., 2008 for a review of theoretical studies). Assuming that both working memory and long-term memory involve the same synapses, a question arises about the dual role of DA in these two types of memory processes. Existing theories of DA modulation of working memory suggest that optimal levels of tonic DA improve stability of neural patterns representing items (or goals) in working memory (Durstewitz et al., 2000a; Cohen et al., 2002), whereas phasic DA works as a gating mechanism to store relevant inputs in the working memory (Braver and Cohen, 1999, for an alternative hypothesis of DA action in the PFC see Dreher and Burnod, 2002). Although more work will be required to make a definite link between these theories and experimental data on long-term memory, we note that our results are consistent with these theories. Indeed, (*i*) optimal levels of tonic DA in our model correspond to enhanced LTP, which is consistent with the idea of storing stable working memory representations in long term memory; and (*ii*) phasic DA is necessary for induction and maintenance of long-term memories which is consistent with the role of phasic DA in reward signaling and gating mechanisms mentioned earlier. In general, our results are in line with the general theory of the role of PFC in executive memory (Fuster, 1995; Miller and Cohen, 2001) in which PFC networks store the task model in long-term memory which is reactivated into working memory each time when the task is encountered (Touzani et al., 2007).

The work presented in this paper is a first step towards addressing the role of phasic and tonic DA in long-term memory in the PFC. Simple phenomenological models of memory formation, such as the one described here, are important to provide a link between electro-physiological data and potentially related cellular mechanisms. Moreover, these models may give an insight into cooperative action of working and long-term memory for the implementation of PFC-dependent cognitive behaviors, and the role of DA in these memory processes.

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