Brief Communication

Dopamine induces LTP differentially in apical and basal dendrites through BDNF and voltage-dependent calcium channels

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The dopaminergic modulation of long-term potentiation (LTP) has been studied well, but the mechanism by which dopamine induces LTP (DA-LTP) in CA1 pyramidal neurons is unknown. Here, we report that DA-LTP in basal dendrites is dependent while in apical dendrites it is independent of activation of L-type voltage-gated calcium channels (VDCC). Activation via NMDAR is critical for the induction of DA-LTP in both apical and basal dendrites, but only BDNF is required for the induction and maintenance of DA-LTP in apical dendrites. We report that dopaminergic modulation of LTP is lamina-specific at the Schaffer collateral/commissural synapses in the CA1 region.

In the hippocampus, afferent inputs to the hippocampus CA1 occur via two major pathways, the temporoammonic and the Schaffer collateral/commissural fibers. Among these, the Schaffer collateral/commissural fibers from the CA3 region synapse on both the apical dendrites in the stratum radiatum (str. radiatum) and the basal dendrites in the stratum oriens (str. oriens).

Studies of long-term potentiation (LTP) in the hippocampal slices both *in vitro* and *in vivo* have shown that the threshold for inducing LTP is lower in basal dendrites in comparison to apical dendrites (Kaibara and Leung 1993; Leung and Shen 1995; Sajikumar et al. 2007; Stramiello and Wagner 2010; Sajikumar and Korte 2011a). The CA1 region receives a variety of neuromodulatory inputs including the dopaminergic, cholinergic, and noradrenergic pathways (Otmakhova and Lisman 2000; Leung et al. 2003), and the distributions of these neuromodulatory inputs are not uniform. For example, the hippocampus receives dispersed cholinergic innervations with the highest density of cholinergic axons in the str. oriens and principal cell layer (Arai et al. 1994; Gasbarri et al. 1994b; Aznavour et al. 2002), and anatomical studies suggest that, not only the str. radiatum but also the str. oriens, is innervated by dopaminergic projections from the meso-limbic-cortical system (Verney et al. 1985; Gasbarri et al. 1994a,b).

The neuromodulatory influences in the str. radiatum and str. oriens regions are also different. One example of a spatially restricted effect of a neuromodulatory neurotransmitter is the action of acetylcholine on the muscarinic acetylcholine receptors. Cholinergic activation by carbachol produces a significantly stronger suppression of synaptic transmission at the CA3-CA1 synapses of the proximal apical dendrites, while being less effective at synapses of the apical tuft (Hasselmo and Schnell 1994). This cholinergic suppression has been shown to enhance associative memory functions (De Rosa and Hasselmo 2000). In neocortical pyramidal neurons, pairing of excitatory post-synaptic potentials (EPSPs) and action potentials (Gordon et al. 2006) leads to the potentiation of synapses at the proximal basal dendrites but

not the distal basal dendrites. In the distal basal dendrites, synaptic potentiation occurs only when synaptic activation (which is strong enough to evoke an NMDA spike) is paired with BDNF application (Gordon et al. 2006). Even within the apical dendrites, the plasticity thresholds for inducing LTP and LTD are different in distal and proximal regions (Parvez et al. 2010; Sajikumar and Korte 2011a).

Persistence of long-term memory depends on the activation of the ventral tegmental area (VTA)/hippocampus dopaminergic connections (Rossato et al. 2009). Dopamine also regulates the expression of proteins essential for the establishment of long-lasting neuronal plasticity like brain-derived neurotrophic factor (BDNF), and this requires NMDA-receptor activity (Kuppers and Beyer 2001). A D1-receptor-dependent increase in BDNF determines the duration of long-term memory (LTM) (Rossato et al. 2009). Cocaine withdrawal is also known to facilitate LTP in medial prefrontal cortex by elevating BDNF levels. After repeated cocaine withdrawal, excitatory synapses onto VTA dopamine neurons become highly sensitive to LTP induction (Pu et al. 2006).

D1-receptor stimulation also induces a long-lasting increase in basal calcium levels from intracellular stores and also via voltage-gated calcium channels (Ming et al. 2006). L-type Ca^{2+} channel immunoreactivity has been observed primarily in the soma, basal, and proximal apical dendrite compartments (Tippens et al. 2008). D1/D5-receptor activation can potentiate L-type Ca^{2+} channels, and this activation by D1/D5-receptor agonists is mediated by cAMP-dependent protein kinase A, as shown in chromaffin cells (Artalejo et al. 1990).

Exogenous application of dopaminergic agonists or dopamine itself can modulate the persistence of LTP in apical dendrites (Huang and Kandel 1995; Navakkode et al. 2007, 2010). However, in contrast to this apical LTP, dopaminergic modulation of LTP within the basal dendrites has not received much attention. Therefore, we set out to investigate whether application of dopamine could induce late-LTP in basal dendrites. We could show that, similar to apical dendrites, dopamine induces a slow onset and long-lasting potentiation (Dopamine induced LTP or DA-LTP). The DA-LTP induction in basal and apical dendrites requires *N*-methyl-D-aspartic acid-receptor (NMDAR) activation. Interestingly, BDNF is only required for the induction and maintenance of DA-LTP in apical dendrites. We also examined whether the L-type voltage-gated calcium

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channels (L-VDCCs) are critical for the induction of DA-LTP in basal dendrites, while L-VDCCs are not required for DA-LTP in apical dendrites.

All procedures were done according to the guidelines of the Institutional Animal Care & Use Committee (IACUC), National University of Singapore, Singapore and Animal Committee on Ethics in the Care and Use of Laboratory Animals of TU-Braunschweig, Germany. We used 101 transverse hippocampal slices (400- μ m thick), prepared from 101 male Wistar rats (6- to 7-wk-old). Slice preparation, incubation, and recordings were conducted according to the protocol reported in our earlier publications (Sajikumar et al. 2005, 2009; Navakkode et al. 2007).

Late-LTP was induced in basal or apical dendrites using a strong tetanization (STET) protocol consisting of three stimulus trains of 100 pulses, 100 Hz duration, 0.2 msec/polarity, and inter-train interval of 10 min (Sajikumar et al. 2005). Four 0.2-Hz-biphasic constant current pulses (0.1 msec/polarity) were used for baseline recording and were delivered at 1, 3, 5, 11, 15, 21, 25, 30, and every 15 min thereafter and continued until 4 h or 6 h.

Dopamine was used at a concentration of 50 μ M (Tocris Cookson). It was dissolved in ACSF containing the antioxidant, ascorbic acid (ROTH), at 1-mM concentration, which had no effect on basal synaptic transmission (Navakkode et al. 2007). AP-5 or nifedipine (Tocris) was used at a concentration of 50 μ M and 10 μ M, respectively (dissolved in ACSF and 0.1% DMSO).

TrkB/Fc, a BDNF scavenger, was used at a concentration of 1 μ g/mL (R&D Systems) (Navakkode and Korte 2012). It was dissolved as a stock solution in 0.1% BSA and aliquoted in small volumes at -20°C .

The average values of the population spike (mV) and slope function of the field-EPSP (mV/msec) per time point were subjected to the Wilcoxon signed rank test when compared within one group or the Mann-Whitney-*U*-test, when data were compared between groups (significant difference was set at $P < 0.05$).

It has been reported earlier that application of D1/D5-receptor agonist or dopamine itself can induce a slow onset potentiation in the apical dendrites of CA1 pyramidal cells (Huang and Kandel 1995; Navakkode et al. 2007; Navakkode and Korte 2012). Consistent with these results, we examined whether or not dopamine can induce slow onset potentiation lasting for at least 4 h (DA-LTP) in apical dendrites ($n = 7$) (Fig. 1B). The fEPSP values showed statistically significant potentiation from 25 min (Wilcoxon test, $P = 0.02$) onwards and then remained stable for the recorded time period of 4 h. Next, we determined whether dopamine can induce long-lasting LTP in the basal dendrites. Similar to apical dendrites, dopamine induced a slow onset, long-lasting LTP for 4 h in basal dendrites ($n = 7$) (Fig. 1E). In all experiments, after a 1-h stable baseline, dopamine (50 μ M) was bath-applied in three pulses for 5 min at 10 min intervals, together with ascorbic acid, an antioxidant, at a concentration of 1 mM.

Figure 1. Dopamine induces LTP in basal and apical dendrites of CA1 pyramidal neurons. (A,D) Schematic representation of electrode location in the apical or basal dendrites of hippocampal slices for recording long lasting potentiation from CA1. Stim 1 represents the stimulating and rec represents the recording electrode in the stratum radiatum. (B,E) Dopamine (50 μ M) was coapplied with the antioxidant ascorbic acid (1 mM) in three pulses for 5-min at 10-min intervals in apical or basal dendrites, respectively. Dopamine induces a slow onset, long-lasting LTP for up to 240 min in apical ($n = 7$) or basal dendrites ($n = 7$). (C,F) Dopamine-induced LTP was maintained for a duration of 120 min, and the stimulation intensity was adjusted to baseline level and recorded a stable baseline for 30 min. A strong tetanization protocol (STET) was applied for inducing late-LTP at 180 min in apical or basal dendrites, respectively, and maintained for 6 h. Potentials decayed to baseline within ~ 300 min in apical ($n = 8$) or basal dendrites ($n = 8$); thus dopamine-induced LTP occludes STET-induced late-LTP. Insets in graphs represent typical field EPSP traces per stimulated input 30 min before (dotted lines), 120 min after (broken line), and 240 or 360 min (continuous line) after LTP induction. Data are expressed as mean SEM. Arrows represent the time point of application of the drug or STET. The cartoon of a neuron presented in each graph shows the site of application of dopamine in apical or basal dendrites. Calibration bar for all analogs: 3 mV/5 msec.

The fEPSP in Figure 1E showed statistically significant potentiation from 25 min (Wilcoxon test, $P = 0.02$) onwards and then remained significant for 4 h (Wilcoxon test, $P = 0.02$). We were interested to know whether DA-LTP shares common mechanisms with tetani-induced LTP in apical and basal dendrites. To address this question, first we induced DA-LTP in apical and basal dendrites and maintained for 120 min (Fig. 1C,F), after which the stimulation intensity was adjusted to baseline level and recorded a stable baseline for 30 min. Strong high frequency stimulation (STET) was delivered at the 180th min to the apical or basal dendrites (Fig. 1C,F), thus electrical induction protocols could induce early LTP but not late-LTP. The LTP in apical and basal dendrites decayed to baseline at 300 min in basal dendrites (Wilcoxon test, $P > 0.05$, $n = 8$) and at 270 min in apical dendrites (Wilcoxon test, $P > 0.05$, $n = 8$).

NMDAR activation was necessary for the induction of DA-LTP in apical dendrites (Navakkode et al. 2010). Consistent with these findings, we found that coapplication of NMDAR antagonist AP-V (50 μ M), along with dopamine, completely abolished LTP in basal dendrites ($n = 8$) (Fig. 2A). In order to address the involvement of calcium channels in DA-LTP, we coapplied dopamine with an L-type VDCC antagonist, nifedipine (10 μ M), either on the apical dendrites or the basal dendrites. As is evident from Figure 2B ($n = 6$), nifedipine did not exert any effects on DA-LTP in apical dendrites, while in basal dendrites, DA-LTP

was completely prevented ($n = 10$) (Fig. 2C). The fEPSP in apical dendrites showed statistically significant potentiation from 25 min onwards compared to its own baseline (Wilcoxon test, $P = 0.02$). In basal dendrites, there was no significant potentiation when compared to the baseline controls (Wilcoxon test, $P > 0.05$).

Dopamine is known to facilitate LTP and long-term memory by increasing BDNF levels in vivo (Rossato et al. 2009). In this context, we investigated whether DA-LTP requires BDNF for its induction and persistence in apical and basal dendrites. To evaluate the role of BDNF, we used a BDNF scavenger, TrkB/Fc (1 μ g/mL). After recording a stable baseline for 30 min, TrkB/Fc was bath-applied initially for 30 min and then coapplied with dopamine (a total of 1 h TrkB/Fc application time) in apical or in basal dendrites. Interestingly, TrkB/Fc prevented DA-LTP in apical dendrites ($n = 8$) (Fig. 3A) but not in basal dendrites ($n = 8$) (Fig. 3B). Next, we examined the effect of BDNF inhibition at two time points, 60 or 180 min, after initial dopamine application (Fig. 3C–F). Continuous inhibition of BDNF by TrkB/Fc starting at 60 or 180 min either in apical or basal dendrites interfered with the maintenance of DA-LTP only in apical dendrites ($n = 8$ for each) (Fig. 3C,E) but not in basal dendrites ($n = 6$ and $n = 8$, respectively) (Fig. 3D,F). TrkB-Fc application decreased the level of potentiation from 105 min onward (U -test, $P = 0.02$) when compared to control DA-LTP in apical dendrites (Fig. 3C) and

Figure 2. Induction requirements of dopamine LTP in basal or apical dendrites. (A) Coapplication of NMDAR antagonist D-AP-V (50 μ M) with dopamine prevents induction of dopamine LTP in basal dendrites ($n = 7$). (B) Coapplication of L-type calcium channel antagonist nifedipine (10 μ M) with dopamine had no inhibitory effect on dopamine-induced LTP in apical dendrites ($n = 6$). (C) The same experiment as in B but repeated in basal dendrites. Here, nifedipine prevents dopamine-induced LTP ($n = 10$). Symbols and traces are as in Figure 1.

Figure 3. Dopamine-induced LTP in basal and apical dendrites have different mechanisms for its persistence. (A,B) After recording a stable baseline of 30 min, TrkB/Fc was bath-applied initially for 30 min and then coapplied with dopamine (a total of 1 h TrkB/Fc application time) in apical or in basal dendrites. TrkB/Fc prevented the induction of LTP in apical dendrites ($n = 8$) but not in basal dendrites ($n = 8$). (C,D) Continuous inhibition of BDNF by TrkB/Fc starting at 60 min after the initial application of dopamine interfered with the maintenance of LTP in apical dendrites ($n = 8$) but not in basal dendrites ($n = 8$). (E,F) Continuous inhibition of BDNF by TrkB/Fc starting at 180 min after the initial application of dopamine interfered with the maintenance of LTP in apical dendrites ($n = 8$) but not in basal dendrites ($n = 8$). Open bar represents the time point of TrkB-Fc application. Symbols and traces are as in Figures 1 and 2.

240 min onward in Figure 3E (U -test, $P = 0.02$). Statistically significant potentiation was observed from 30 min (Wilcoxon test, $P = 0.02$) onward and then remained significant for 4 h or 6 h in the basal dendrites (Fig. 3D,F).

Our results showed that the activation of dopaminergic receptors by dopamine could induce long-lasting LTP in both apical and basal dendrites of the CA1 pyramidal cells, and these forms of LTP are similar in their mechanism to that of electrically induced late-LTP (Huang and Kandel 1995; Sajikumar and Frey 2004).

Although DA-LTP in both apical and basal dendrites required NMDAR activation, similar to that of electrically induced late-LTP (Arai et al. 1994; Haley et al. 1996), we observed that, in addition to NMDAR, L-type VDCC activation was also required for DA-LTP in basal dendrites. These findings are in agreement with the earlier report that the threshold for inducing LTP differed in the CA1 pyramidal neurons. For instance, a weak stimulation in distal apical dendrites resulted in protein synthesis-independent LTP, while the same stimulation resulted in long-lasting protein

synthesis-dependent late-LTP in proximal apical dendrites (Sajikumar and Korte 2011a). The plasticity threshold in str. oriens may differ in comparison to str. radiatum due to its morphology and biophysical properties. For instance, GABAergic and retrograde messenger nitric oxide (NO) requirements are less in str. oriens compared to str. radiatum (Toth and Freund 1992; Haley et al. 1996). These differences could play an important role in the integration of afferent inputs in CA1 pyramidal neurons. By knowing the difference in apical and basal dendrites, one would expect that dopamine modulation might be stronger in basal dendrites, and it might induce a higher percentage of potentiation. However, our studies showed that DA-LTP in both regions was of similar magnitude, indicating that dopamine might exert its effects almost similarly in the two regions with some exceptions in induction and maintenance (see below).

It was hypothesized that D1/D5-receptors might enhance potentiation by three different mechanisms (Otmakhova and Lisman 1996; Raman et al. 1996). On the one hand, dopamine might cause an enhancement of LTP by increasing depolarization (Yang and Seamans 1996) and, on the other hand, by enhancing the NMDA receptors that are critical for LTP induction (Raman et al. 1996). In addition, substantial biochemical evidence suggests that cAMP metabolism is powerfully controlled by neuromodulators (Cooper et al. 1995). Apart from the effect of neuromodulators, induction of LTP also requires calcium influx into post-synaptic neurons through ligand-gated NMDA-receptors and also through voltage-dependent calcium channels. Nifedipine is known to substantially reduce LTP in the presence of AP-5, and this points to the fact that L-type VDCCs participate in the induction of NMDA-receptor-independent LTP in the CA1 area (Grover et al. 2009). As VDCCs and NMDA receptors underlie two forms of LTP in the hippocampus (Artalejo et al. 1990), dopamine might act together with the activation of NMDAR and L-type VDCCs or in an NMDA-receptor-dependent manner. Our results revealed that DA-LTP induction in basal dendrites required both NMDAR and L-type VDCCs, while apical dendrites were independent of L-type VDCCs for DA-LTP. This view is strengthened by our earlier findings that dopamine-LTP in apical dendrites was NMDA-receptor-dependent (Navakkode et al. 2010), and synergistic activity of D1/D5 and NMDAR function was required for the induction and maintenance of DA-LTP apical dendrites (Navakkode et al. 2007, 2010). It is also important to note that, as reported, dopaminergic function in hippocampal CA1 is to modulate synaptic responses rather than the activation of the machinery required to induce protein synthesis-dependent L-LTP (Mockett et al. 2004). This discrepancy in the mechanisms of dopaminergic activation has been addressed in our recent reports (Navakkode et al. 2007, 2010). Similar to NMDA-receptor-dependent LTP, long-term memory also depends on the activation of VTA/hippocampus dopaminergic connections and can be specifically modulated by manipulating this system. Both BDNF and TrkB-receptors are expressed by the dopaminergic neurons and dopamine modulates LTP and LTM by regulating the expression of proteins like BDNF (Rossato et al. 2009) and PKM ζ (Navakkode et al. 2010), which are essential for the establishment of long-lasting plasticity (Korte et al. 1998; Ling et al. 2002).

Our studies show that inhibiting BDNF-mediated actions prevents DA-LTP only in apical dendrites without affecting the induction and maintenance of DA-LTP in basal dendrites. Thus, the L-type VDCC and NMDAR-dependent DA-LTP in basal dendrites follows a signaling pathway independent of BDNF, while the NMDA-receptor-dependent DA-LTP in apical dendrites is dependent on BDNF. It had been reported earlier that BDNF inhibition had differential effects on tetani-induced and theta burst stimulation (TBS)-induced LTP (Chen et al. 1999). Importantly, it was suggested that endogenous BDNF was required for a limited time

period only shortly before or during LTP induction but not over the whole process of LTP. Our findings are consistent with this study for the requirement of BDNF for induction of DA-LTP. In contrast, we report that BDNF inhibition 60 min or 180 min after the establishment of DA-LTP could also prevent its maintenance in apical dendrites. These results support earlier findings that continuous activation of BDNF receptors is necessary for the maintenance of certain forms of late-LTP (Huang and Kandel 1995) and its associativity from tetanized synapses to depressed synapses (cross-tagging) (Sajikumar and Korte 2011b). In addition, continued activation of BDNF receptors was also necessary for the generation of the long-lasting form of LTP induced by glutamatergic and cholinergic activation (Navakkode and Korte 2012).

In general, our data support that tetani-induced late-LTP and dopamine-induced LTP have the following similarities: (1) NMDAR activation and protein synthesis (Navakkode et al. 2010); (2) the BDNF requirement for the long-lasting maintenance of LTP in apical dendrites; and (3) associativity and cooperativeness between strongly activated and weakly activated synapses. Although, associativity is expressed in dopamine-induced LTP (Navakkode et al. 2010), it remains to be investigated how long the cooperative interaction can be maintained with DA-LTP.

The reduced expression of BDNF within the substantia nigra accompanies the deterioration of dopaminergic neurons in Parkinson's disease (PD) patients (Baquet et al. 2005), and activation of L-type calcium channels is required for dopamine release (Mendez et al. 2011). Understanding the mechanism of action of dopamine in different regions of the brain could, therefore, help us to elucidate the etiology of neurodegenerative diseases like PD. The existence of such apical and basal synaptic transmission with different properties has been suggested to provide a higher sensitivity and diversity for synaptic plasticity in the hippocampus (Leung and Shen 1995). The physiological relevance of the differential distribution of neuromodulators, their action, and their differences in LTP threshold is not known. We, therefore, hypothesize that a difference in the balance of synaptic plasticity between different regions might account for how system-relevant information is coded in neuronal networks for storing memory engrams effectively. In addition, the alternative mechanisms used for neuromodulation in different regions might also render neuroprotection and reduce vulnerability to neurodegenerative diseases.

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The e-mail address for co-corresponding author Sheeja Navakkode in the above-mentioned article includes a typo. The correct e-mail address is: sheejanavakkode@yahoo.co.uk.

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Sheeja Navakkode, Sreedharan Sajikumar, Martin Korte, et al.

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