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# D4 Receptor Activation Differentially Modulates Hippocampal Basal and Apical Dendritic Synapses in Freely Moving Mice

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**Activation of D4 receptors (D4Rs) has been shown to improve cognitive performance, potentially affecting synaptic strength. We investigated the D4R agonist PD 168077 (PD) in hippocampal CA1 of freely moving mice. We electrically stimulated in stratum oriens (OR) or radiatum (RAD) and evoked local field potentials (LFPs). Intraperitoneally injected PD dose-dependently and reversibly attenuated LFPs for longer time in basal (OR) than apical (RAD) dendrites. High-frequency stimulation induced LTP that was stronger and more stable in OR than RAD. LTP lasted at least 4 h during which the paired-pulse ratio remained reduced. A PD concentration not affecting synaptic transmission was sufficient to reduce LTP in OR but not in RAD. A PD concentration reducing synaptic transmission reduced the early phase LTP in OR additionally and the late phase LTP in RAD exclusively. Furthermore, cell type-specific expression of mCherry in DATCre mice generated fluorescence in dorsal CA1 that was highest in lacunosum moleculare and similar in OR/RAD, indicating that midbrain dopaminergic fibers distribute evenly in OR/RAD. Together, the D4R-mediated modulation of hippocampal synaptic transmission and plasticity is stronger in OR than RAD. This could affect information processing in CA1 neurons, since signals arriving via basal and apical afferents are distinct.**

**Keywords:** dopaminergic input, LTP, PPR, presynaptic mechanism, VTA

## Introduction

Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain, where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake and endocrine functions (Missale et al. 1998; Beaulieu and Gainetdinov 2011; Lisman et al. 2011). In recent years, evidence accumulated that hippocampal D1-like receptors (D1/5R) are involved in learning and memory (Moncada and Viola 2007; Rossato et al. 2009; Wang et al. 2010), in particular for associative learning (Ortiz et al. 2010) and the formation of long-lasting, e.g., episodic memories (>4 h) (Bethus et al. 2010). Requirement of DA for spatial and contextual information processing seems to apply to human beings as well, as levodopa dose-dependently improved the performance of elderly persons in an episodic memory paradigm at least for 6 h (Chowdhury et al. 2012).

Many pharmacological experiments have addressed the dopaminergic modulation of synaptic transmission and plasticity in the hippocampus, mainly in apical dendrites. Recordings in distinct CA1 layers demonstrate DAergic modulation of the direct cortical pathway to CA1 in stratum lacunosum moleculare (SLM) with a possible contribution from inhibitory networks (Otmakhova and Lisman 1999; Ito and Schuman 2007). At the Schaffer collateral synapses in RAD, D1/5R activation increases the magnitude of early phase (mins) long-term potentiation (LTP) (Otmakhova and Lisman 1996) and stabilizes late phase LTP (h) in vitro (Frey et al. 1988, 1993; Huang and Kandel 1995; Navakkode et al. 2012) and in vivo (Swanson-Park et al. 1999; Lemon and Manahan-Vaughan 2006). In contrast, the effects of D2-like receptors (D2R, D3R, D4R) have been less well explored. Still, D2-like receptor agonists can reduce basal synaptic transmission in CA3–CA1 synapses in rat slices (Huang and Kandel 1995) and in perforant path-dentate gyrus granule cell synapses in freely moving rats (Manahan-Vaughan and Kulla 2003). Recently, we found that the D4R agonist PD168077 (PD) impairs NMDA receptor-dependent early phase LTP in oriens (OR) but not in radiatum (RAD) by reducing the NMDA currents during LTP induction in mouse hippocampal slices (Herwerth et al. 2012). It is important to investigate this input difference in vivo, since basal and apical CA1 dendrites are differentially innervated, receiving distinct information via recurrent collaterals of CA1 neurons, via ipsilateral CA2 neurons, via ipsi- and contralateral CA3 neurons and via the alvear group of entorhinal afferents (Dong et al. 2008; Neves et al. 2008; Shinohara et al. 2012; Takács et al. 2012). Behaviorally relevant signals arriving in CA1 are modulated by DARs including D4Rs whose deficiency in knockout mice exhibit reduced exploration of novel stimuli (Dulawa et al. 1999) and whose activation via agonist improves cognitive performance (Bernaerts and Tirelli 2003; Sood et al. 2011). Furthermore, PD dampens cognitive dysfunction in an animal model relevant to schizophrenia (Sood et al. 2011), suggesting the involvement of D4Rs also in other cognitive deficit symptoms including attention-deficit hyperactivity disorder and autism (Furth et al. 2013).

Lisman and Grace developed the concept that the hippocampus and the midbrain dopaminergic neurons of the ventral tagmental area (VTA) form a functional loop, which controls information entry into long-term memory (Lisman and Grace 2005). Besides dopaminergic inputs arising from VTA (Scatton et al. 1980; Gasbarri et al. 1994; Gasbarri et al. 1997), noradrenergic inputs originating from locus coeruleus may also release DA within the hippocampus (Smith and Greene 2012). To extend our previous attempts to examine the distribution of VTA/substantia nigra (SN) fibers in hippocampal CA1, which had used a reporter mouse that expresses EGFP in dopaminergic fibers (Herwerth et al. 2012), we now expressed mCherry specifically in the dopaminergic neurons in the VTA/SN of DATCre mice (Parlato et al. 2006).

Our present work in freely moving mice investigated the function of D4Rs on basal synaptic transmission in hippocampal CA1 both in OR and RAD and also examined the modulation of LTP by a D4R agonist in both pathways. At the same time, we monitored paired-pulse ratio (PPR) changes to consider the involvement of pre/postsynaptic mechanisms. Furthermore, the VTA/SN originated dopaminergic fibers terminating in dorsal hippocampus were quantified in CA1 sublayers in DATCre mice.

## Materials and Methods

Experimental procedures were in accordance with the animal welfare guidelines of the Max Planck Society, the Regional Board Karlsruhe (35-9185.81/G-273/12), and the "European Union's Directive 86/609/EEC."

### *Animals, Surgery, and Implantation of Electrodes*

Seven-week-old C57BL/6N mice were deeply anesthetized with a mixture of Ketamine and Xylazine (K/X mixture; Ketamine, 65 mg/kg, Xylazine, 14 mg/kg). After injection, mice were placed in a stereotaxic frame. The distance ($D$) between bregma and lambda was measured after opening the scalp and removing the soft tissue with 15% $H_2O_2$.

Two mini-screws were fixed above the cerebellum. One served as reference and the other one served as ground wire. The positions for a bipolar stimulation electrode and two recording electrodes were marked on the same hemisphere according to the stereotaxic coordinates (Paxinos and Franklin, 2001). Due to differences in $D$, the position of the stimulation (S) electrode anterior-posterior (AP) to bregma was obtained by $AP_S = 2.0 \times D/4.2$ mm, and the middle-lateral (ML) distance was obtained by $ML_S = 2.3 \times D/4.2$ mm (for recording (R) electrodes, $AP_R = (2.0 \times D/4.2) - 0.05$ mm; $ML_R = 1.7 \times D/4.2$ mm). Two 0.5 mm holes in diameter were drilled through the marked points. For stimulation, 2 insulated tungsten wires, serving as anode and cathode (same length, single wire diameter, 52 µm; California Fine Wire, USA) with 80–100 µm distance between the tips, were lowered by a motorized manipulator (Luigs & Neumann, Ratingen, Germany). For recording, 2 tungsten wires, one being longer (~250 µm), were placed in OR and RAD. The final depths for stimulation and both recording electrodes were determined by online monitoring depth profiles of evoked local field potentials (LFPs), that is, negative response in OR and positive response in RAD when stimulation electrode was implanted in OR, and reversed deflections of LFPs when stimulation electrode was implanted in RAD (Fig. 1), consistent with depth profiles obtained during electrode implantation in mice and rats from other research groups (Kaibara and Leung 1993; Leung and Péloquin 2010; Shires et al. 2012; Gruart et al. 2015). To further confirm the correct positions, a full range of input/output (IO) was generated before the electrodes were permanently fixed with a small amount of dental acrylic (weight, ~0.5 g including pins).

Surgical wounds were sutured, and animals were supplied with softened, wet food during the recovery period and singly housed. Mice were kept on a 12-h light/dark cycle. With access to food and water ad libitum, the animals recovered for at least one week before recording in the inactive phase.

### *Data Acquisition and Analysis*

In the evening before the experimental day, animals were put in the recording chamber (50 cm diameter round arena, 50 cm high) for habituation. On the experimental day, animals were briefly exposed to isoflurane to alleviate the stress when connecting the pins to the miniature headstage (weight, ~1 g, npi electronic GmbH, Tamm, Germany) for differential measurement of LFPs via 2 extracellular amplifiers (EXT-02F, npi electronic GmbH). The miniature headstage also allowed extracellular stimulation with a stimulus isolator (A365, WPI, Sarasota, FL, USA) and the acquisition of motor activities monitored via a 3D accelerometer. The latter feature combined with continuous EEG recordings permitted us to distinguish sleep from active wakefulness during our recording sessions. Furthermore, we excluded that electrical tetanization during LTP induction triggered seizures. LFP signals were filtered between 0.3 and 500 Hz, digitized at 10 kHz (ITC-16, Patchmaster, HEKA Elektronik, Lambrecht, Germany), and 50 Hz noise was removed by Hum Bug Noise Eliminators (AutoMate Scientific, Inc., Berkeley, CA, USA). Evoked LFPs were stored on PCs, and their slopes were analyzed based on the middle one-third of the rising phase (Fitmaster, HEKA Elektronik, Lambrecht, Germany). At the beginning of each recording, IO curves were generated by applying stimulation voltages with both polarities. To evaluate changes in synaptic efficacy, a stimulus strength eliciting 35–40% of maximum slope was used as test pulse given every 30 s. Toward the end of each 30-min period, 10 paired pulses with 50 ms interstimulus interval (ISI) were generated to examine the PPR. Two trains of high-frequency stimulation (HFS, 50×, 100 Hz, 100 µs pulse width, same intensity as test pulse) separated by 5 min were used to induce LTP. With this protocol, LTP could be induced that lasted at least 24 h as described previously (Buschler et al. 2012).

### *Drug Preparation and Injection*

Normal saline (NS, 0.9% NaCl) was used as vehicle for the control group. D4R agonist PD 168077 maleate (PD, Biotrend chemicals AG, Switzerland) was dissolved in NS to reach the concentrations of 1 and 0.25 mg/mL. Both control and different PD groups received 0.1 mL/10 g intraperitoneally (i.p.) injections when a stable baseline was acquired. In the LTP experiments, NS and PD were injected 30 min before induction.

### *Histological Analysis*

After recording, animals were deeply anesthetized with K/X mixture, electrical lesions were induced twice (20 µA, 10 s) for each single tungsten wire separately. Subsequently, the mice were perfused with phosphate-buffered saline (PBS) followed by 4% paraformaldehyde (PFA). The brains of the mice were collected and incubated in a mixture of PBS and 4% PFA (1:1) over night. On the following day, the brains were sliced coronally at 80 µm thickness and mounted on gelatinized glass slides and classical Nissl staining was performed to verify electrode locations.

### *Stereotaxic Injections*

Heterozygous transgenic mice (Tg(DAT-iCre)9075Gsc, also called DATCre; (Parlato et al. 2006)) expressing the Cre recombinase under control of the DA transporter gene contained in a bacterial artificial chromosome were anesthetized with K/X mixture on P21 and placed in a stereotaxic frame. The scalp was shaved, opened, and swabbed before drilling a hole above the ventral midbrain (anterior-posterior, −2.5 mm, lateral, ±0.8 mm). About 500 µL of Cre-inducible recombinant rAAV-EF1a-DIO-hChR2(H134R)-mCherry was loaded into a glass capillary pulled with a tip diameter of 0.3 µm and then bilaterally injected into the VTA/SN (dorsal-ventral, −4.2 mm).

### *Immunohistochemistry, Fluorescence Imaging, and Analysis*

Three weeks after stereotaxic injection of AAV, the DATCre mice were perfused with PBS followed by 4% PFA. Brains were removed and postfixed with 4% PFA for 2 h at room temperature. About 50-µm-thick sections were sliced and immersed in PBS, blocked for 1 h with 10% normal goat serum (NGS) in 1% Triton X and incubated overnight at room temperature with mouse anti-NeuN (Neuronal Nuclei) (Chemicon) and rabbit anti-DsRed (Clontech), which also recognizes mCherry, both at 1:1000 in 1% NGS, 0.3% Triton X. On the second day, brain sections were rinsed with PBS, incubated 2 h at room temperature with FITC-conjugated anti-mouse and CY3-conjugated anti-rabbit secondary antibodies (both at 1:500, Jackson ImmunoResearch), washed with PBS, mounted on slides, and coverslipped with Mowiol. Confocal stack images were acquired with a ×20 objective (aperture, 0.7) at a Leica SP2 confocal microscope. Images were processed in Image J, and pixel intensity of the axons was measured as described before (Grider et al. 2006).

### *Statistics*

Two-sample Kolmogorov–Smirnov test (K-S test) was used to test differences in the IO efficiency. Repeated-measures analysis of variance (ANOVA) was used to compare the slope of LFPs after injection/HFS

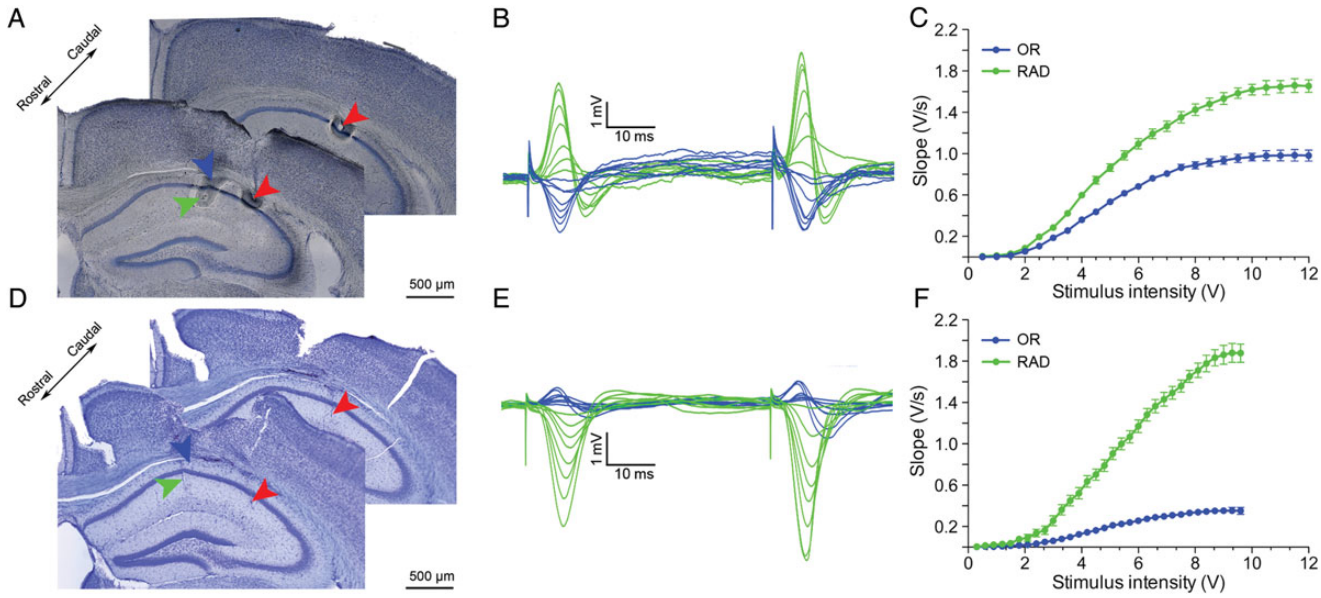


**Figure 1.** Placement of electrodes, representative traces of LFPs and IO curves. (*A*,*D*) Nissl staining following electrical lesions illustrates the locations of bipolar stimulation electrode (red arrow heads, *A*, OR; *D*, RAD), recording electrode in OR (blue arrow head) and recording electrode in RAD (green arrow head). (*B*,*E*) Representative, color-coded traces of evoked responses during acquisition of the IO when the stimulation electrode placed in OR (*B*) and RAD (*E*). (*C*,*F*) IO curves based on absolute values of slope against stimulus intensity when stimulating in OR (*C*, $n = 32$) and RAD (*F*, $n = 32$). Significance was tested by two-sample K-S test (see Results).

for NS versus PD groups, and post hoc *t*-test to compare slopes at distinct time points. Two-tailed paired *t*-test was used to compare the PPR after injection and/or HFS with control (before injection). Two-tailed unpaired *t*-test was adopted to compare the difference of PPR after normalization to before injection between NS and PD groups. One-way ANOVA followed by Dunnett's multiple comparison test was used to compare the density of dopaminergic projections in different compartments of dorsal hippocampus. Error bars shown in the figures indicate standard error of the mean. The level of significance was set to $P < 0.05$.

## Results

### *Input/output Relationships Indicate Higher Synaptic Efficiency in Apical than Basal Dendrites*

Here, we recorded LFPs in freely moving mice with 2 tungsten electrodes in OR and RAD while stimulating with one bipolar electrode in OR or RAD. With this configuration (Fig. 1*A*,*D*), we recorded negative LFPs on the same site of stimulation and LFPs with opposite deflections on the other site of stratum pyramidale (Fig. 1*B*,*E*). When suprathreshold stimulus intensities were applied either in OR or RAD (Fig. 1*C*,*F*), the output (absolute slope of the LFP) was stronger in RAD than in OR (green vs. blue in Fig. 1*C*,*F*; K-S test, $P < 0.01$). This output difference was more pronounced for stimulations in RAD than OR (Fig. 1*F* vs. *C*; K-S test, $P < 0.01$). Also, the input/output relationship was steeper for RAD than OR (Fig. 1*C*,*F*; K-S test, $P < 0.01$), and consequently the stimulus intensity to saturate LFPs was lower in RAD than in OR (Fig. 1*C*,*F;* 9.6 vs. 12 V). Finally, the slope of maximally evoked LFPs were about 2-fold in RAD (Fig. 1*F*, green) compared with OR (Fig. 1*C*, blue; K-S test, $P < 0.01$; OR, $n = 32$, RAD, $n = 32$).

These observations indicate a lamina-specific synaptic efficiency difference in hippocampal CA1 of mice.

### *PD Dose-Dependently and Transiently Reduces Evoked LFPs in Apical and Basal Dendrites*

To find out whether i.p. injection of the D4 agonist PD 168077 affects synaptic transmission in hippocampal apical and/or basal CA1 dendrites of freely moving mice, we evoked LFPs by single-pulse stimulation for 1 h (baseline) before injecting PD or NS. First of all, we chose a concentration of PD (10 mg/kg) that had been shown to improve memory performance in contrast to lower concentrations (Bernaerts and Tirelli 2003; Sood et al. 2011). Relative to baseline, PD reduced the slope of LFPs in both pathways, stronger in OR than in RAD (Fig. 2*C*; maximal effects, OR, ~15% at 45 min; RAD, ~10% at 20 min; $^{*}P < 0.05$; OR: NS, $n = 6$; PD, $n = 7$; RAD: NS, $n = 6$; PD, $n = 7$). 30 min after injection of PD, the robust effect on the slope of the LFP in OR shifted the peak of the LFP to the right, which was not similarly obvious for the LFPs in RAD (Fig. 2*A*). Also, the PD-mediated effects lasted longer in OR (more than 1 h) than in RAD (15 min).

To consider whether presynaptic mechanisms were involved in the reduction of LFPs by PD (10 mg/kg), we monitored the PPR (50 ms ISI) every half an hour during the 5-h recording sessions. Before i.p. injection, PPR was similar in OR and RAD (OR, $1.55 \pm 0.05$, $n = 13$; RAD, $1.67 \pm 0.07$, $n = 13$). In both pathways, PPR remained stable in the NS group (OR: $n = 6$; RAD: $n = 6$) but increased in the PD group as long as the slope of LFPs was decreased (Fig. 2*B*; $^{\#}P < 0.05$; OR, $n = 7$; RAD, $n = 7$). Consistently, a transient but significant PPR difference was found between NS and PD (10 mg/kg) treated groups (Fig. 2*B*; $^{*}P < 0.05$).

A lower dose of PD (2.5 mg/kg) changed neither slope nor PPR (50 ms ISI) of evoked LFPs. Thirty minutes after injection, the slope of the LFP relative to baseline was $99.84 \pm 0.96\%$ in OR ($n = 5$) and $101.67 \pm 1.49\%$ in RAD ($n = 6$) and the PPR was $98.40 \pm 1.38\%$ in OR ($n = 5$) and $100.18 \pm 0.83\%$ in RAD ($n = 6$) (Fig. 3*B*,*C*).

Overall, only a high dose of the D4 agonist reduced evoked LFPs and increased PPR stronger in OR than in RAD. In both pathways, these PD-mediated effects were reversible.

### *LTP Differs in Basal versus Apical Dendrites*

In freely moving rats, LTP is more easily induced in basal dendrites (OR) than in apical dendrites (RAD) (Leung and Shen

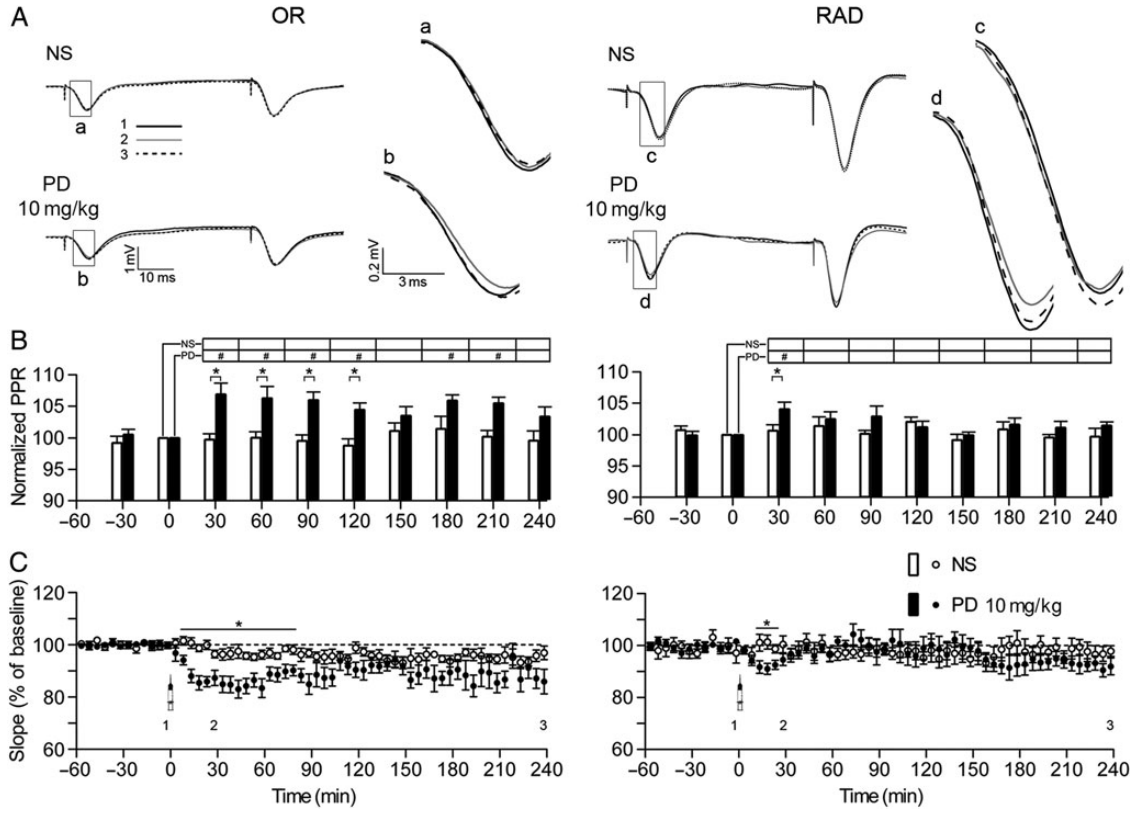


**Figure 2.** D4R agonist transiently reduces basal synaptic transmission both in basal (OR, left) and apical (RAD, right) dendrites. (*A*) Averaged (×10), representative traces acquired before injection (1) and 30 (2)/240 min (3) after injection of NS or PD. Insets show magnification of boxed regions. (*B*) PPRs at time points corresponding to the time course in (*C*) and normalized to values obtained before injection of NS or PD (*$P < 0.05$, unpaired *t*-test, differences between NS and PD; $^{\#}P < 0.05$, paired *t*-test, different from PPR before injection). (*C*) Syringes indicate time of injection, horizontal lines indicate duration of significance (*$P < 0.05$, repeated-measures ANOVA, post hoc *t*-test). (*B*,*C*) NS, $n = 6$; PD, $n = 7$ for both OR and RAD.

1995). Consistently, stronger LTP was induced in OR than in RAD of freely moving mice using 2 trains of HFS at 100 Hz 30 min after NS injection (Fig. 3*C*, $P < 0.01$, OR, $n = 7$; RAD, $n = 7$). In particular, the potentiation during the first 30 min after induction (early phase LTP) was stronger in OR than RAD (~180 vs. ~145% relative to baseline; $P < 0.01$). Early phase LTP in OR did not decline and persisted at least for 4 h (late phase LTP, Fig. 3*C*), while early phase LTP in RAD gradually declined within 90 min before stabilizing at a potentiated level (Fig. 3*C*; $P < 0.01$). In NS and following LTP induction, the PPR was reduced for up to 4 h after induction in both pathways (Fig. 3*B*, $^{\#}P < 0.05$; OR, $n = 7$; RAD, $n = 7$). Notably, the PPR changes were not stronger in OR than in RAD (Fig. 3*B*; e.g., at 270 min, $P > 0.05$) even though stronger LTP was induced in the OR pathway.

Thus, in OR early and late phase LTP had comparable magnitudes, whereas in RAD early phase LTP was higher than late phase LTP. In both pathways, the PPR similarly remained reduced throughout LTP expression.

### *PD Reduces LTP in OR and RAD with Distinct Time Courses*

In hippocampal slices, PD modulates early LTP (40 min) in OR but not in RAD (Herwerth et al. 2012). To address the modulation of LTP by this D4R agonist in freely moving mice, we tested different doses of PD.

A low dose of PD (2.5 mg/kg), which had no effect on basal synaptic transmission both in OR and RAD, did not affect early phase LTP in OR but significantly reduced late phase LTP (Fig. 3*C*; *$P < 0.05$; OR, $n = 5$). The PPR was reduced during the early phase LTP (Fig. 3*B*; $^{\#}P < 0.05$; OR, $n = 5$), similar to NS, but the PPR was no longer significantly reduced when the late phase LTP was reduced relative to NS. In RAD, PD (2.5 mg/kg) had no obvious effect on both early and late phase LTP, and the PPR was reduced as observed for NS (Fig. 3*B*,*C*).

A high dose of PD (10 mg/kg), distinct from the low dose, also reduced early phase LTP in OR (Fig. 3*C*, *$P < 0.05$; OR, $n = 7$). Consequently, early and late phase LTP were similarly reduced in OR in the presence of the high dose of PD. Nonetheless, the PPR remained significantly reduced during early phase but not during late phase LTP (Fig. 3*B*; $^{\#}P < 0.05$; $n = 7$). In RAD, the high dose of PD did not modulate early phase LTP (Fig. 3*C*, RAD, $n = 6$), and the PPR remained significantly reduced (Fig. 3*B*; $^{\#}P < 0.05$, $n = 6$). During the subsequent 3–4 h of recording, the PPR became different between NS and PD (180–270 min, Fig. 3*B*, right panel, *$P < 0.05$), LTP decreased but a late phase LTP remained ($P < 0.01$, relative to baseline).

In summary, a low dose of PD, which did not affect the basal synaptic transmission exclusively reduced late phase LTP in the basal dendrites but had no effect on LTP in apical dendrites. A high dose of LTP, which reduced basal synaptic transmission decreased early and late phase LTP in basal dendrites and exclusively late phase LTP in apical dendrites. The reducing effects on LTP occurred in part without modulation of PPR.

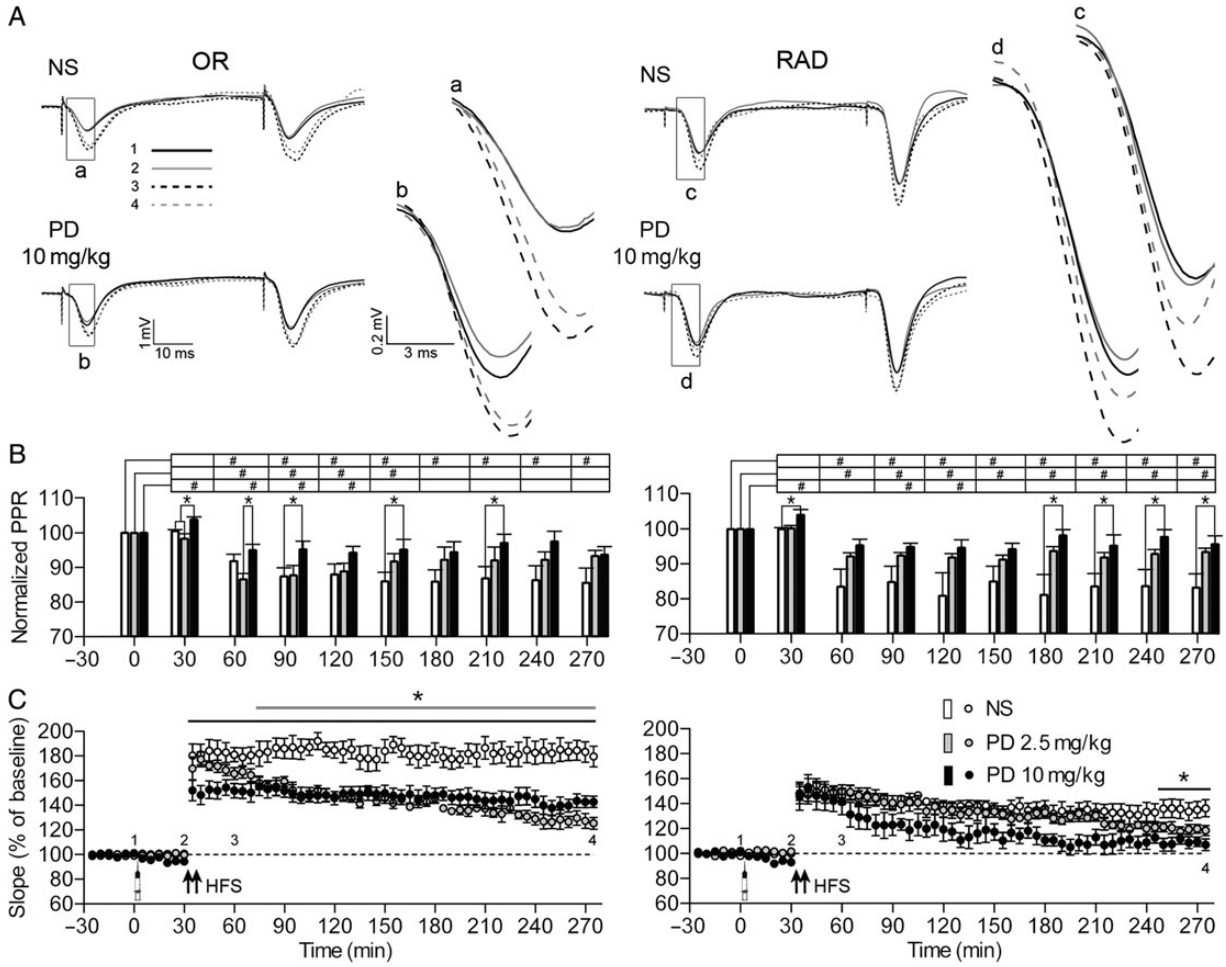


**Figure 3.** D4R agonist differentially modulates LTP in basal (OR, left) and apical (RAD, right) dendrites. (*A*) Averaged (×10), representative traces acquired before injection (1), before HFS (2), and 30 (3)/240 min (4) after injection of NS or PD (10 mg/kg). Insets show magnification of boxed regions. (*B*) PPRs at time points corresponding to the time course in (*C*) and normalized to values obtained before injection of NS or PD (*$P < 0.05$, unpaired *t*-test, differences between NS and PD; $^{\#}P < 0.05$, paired *t*-test, difference from PPR before injection). (*C*) Syringes indicate time of injection, arrows indicate 2 trains of HFS (separated by 5 min), horizontal lines indicate duration of significant difference between the NS group and PD (10 mg/kg, black line), lower dosage PD (2.5 mg/kg, grey line) (*$P < 0.05$, repeated-measures ANOVA, post hoc *t*-test). (*B*,*C*: OR: NS, $n = 7$; PD 2.5 mg/kg: $n = 5$; PD 10 mg/kg: $n = 7$; RAD: NS, $n = 7$; PD 2.5 mg/kg: $n = 6$; PD 10 mg/kg: $n = 6$).

### *Homogeneous VTA/SN Dopaminergic Fiber Distribution in OR and RAD of Dorsal Hippocampus*

The distribution of dopaminergic fibers in the dorsal hippocampal CA1 region was quantified by immunohistochemical staining with antibodies against mCherry and neuronal nuclei (NeuN) in DATCre mice injected with a mCherry-expressing virus in VTA/SN (Fig. 4). The axon density was compared between OR, RAD, and SLM in coronal and sagittal slices by analyzing the pixel intensity within the 3 layers. We analyzed 11–19 coronal and 21–24 sagittal sections per mouse (coronal, $n = 3$ mice; sagittal, $n = 3$ mice). The total analyzed area per section was 0.5–1.6 $mm^2$ in OR, 0.2–1.8 $mm^2$ in RAD, and 0.03–1.3 $mm^2$ in SLM. In dorsal hippocampal CA1, the highest density of dopaminergic fibers was present in SLM. Compared with SLM (chosen as reference and normalized to 1.0), the fiber densities in OR and RAD were lower but comparable with each other (Fig. 4*D*, $F_{2,6} = 20.63$, $P < 0.01$, $^{**}P < 0.01$ for OR vs. SLM and RAD vs. SLM, $P > 0.05$ for OR vs. RAD; Fig. 4*H*, $F_{2,6} = 11.34$, $P < 0.01$, $^{**}P < 0.01$ for OR vs. SLM, $^{*}P < 0.05$ for RAD vs. SLM, $P > 0.05$ for OR vs. RAD).

In summary, dopaminergic inputs originating from VTA/SN appear to be homogeneously distributed in OR and RAD, and are highest in SLM in dorsal hippocampal CA1.

## Discussion

We activated D4Rs in freely moving mice and found basal synaptic transmission to be unchanged with a low dose of PD (2.5 mg/kg) but reduced with a high dose (10 mg/kg). This reduction persisted longer in OR than in RAD. The low dose of PD impaired late phase LTP in OR without affecting LTP in RAD, while the high dose of PD reduced both early and late phase LTP in OR but only late phase LTP in RAD. Based on the simultaneously recorded PPR, the modulatory effects of the D4 agonist in the 2 CA1 compartments OR and RAD appear to involve both pre- and postsynaptic mechanisms. As we found comparable dopaminergic innervation in the dorsal hippocampal OR and RAD, the effects of PD could potentially be mediated by DA released from dopaminergic neurons originating in the VTA and/or SN.

### *Signal-Guided Electrode Positioning*

Our approach to locate 2 recording electrodes on both sides of stratum pyramidale ensured precise positioning of recording and stimulation electrodes in OR and RAD already during implantation, since the intended negative and positive LFPs were

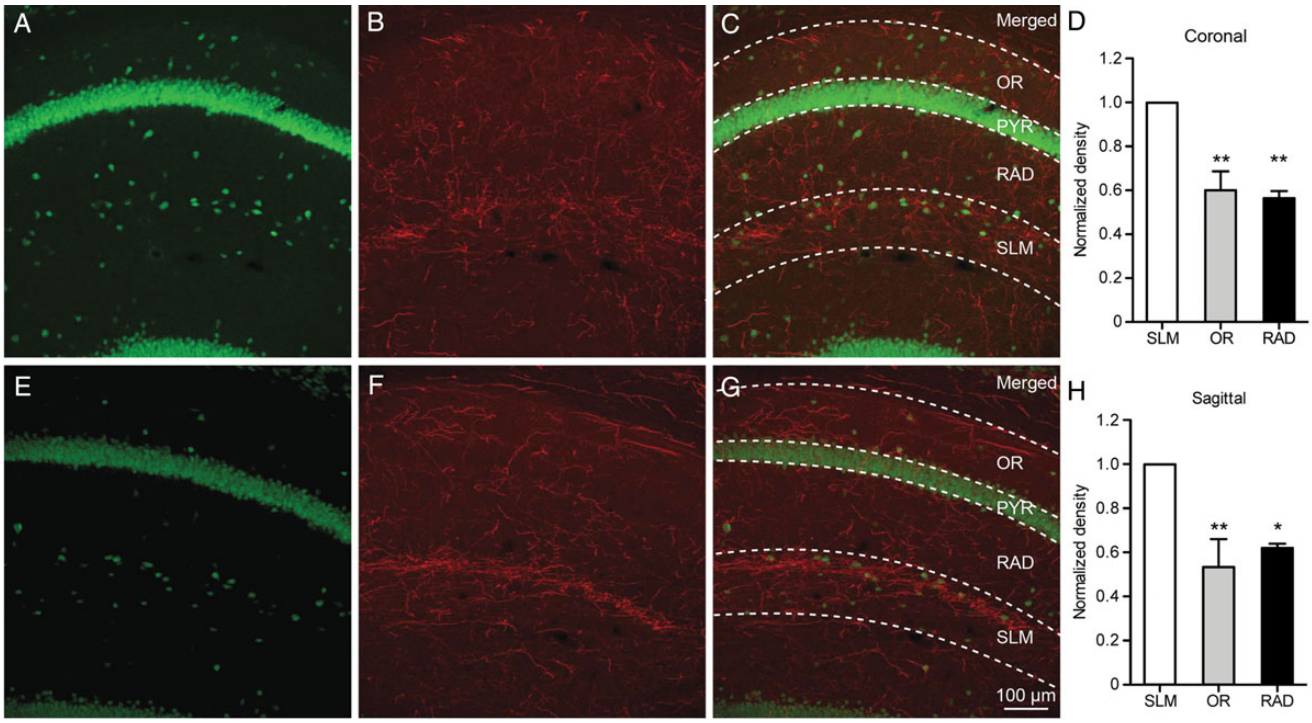


**Figure 4.** VTA/SN originated dopaminergic projections in dorsal hippocampus of DATCre mice (*A*, *B*, *C*: coronal sections; *E*, *F*, *G*: sagittal sections). (*A*,*E*) Antibody staining against neuron nuclei (NeuN) identifies the pyramidal cell layer and (*B*,*F*) antibody staining against mCherry indicates the dopaminergic fibers arising from VTA/SN. (*C*,*G*) Merged images with broken lines showing the CA1 compartments that were analyzed (OR, RAD, SLM). (*D*,*H*) Comparison of dopaminergic fiber density in OR and RAD relative to the density in SLM in coronal (*D*) and sagittal slices (H) (**$P < 0.01$, *$P < 0.05$, $n = 3$ mice for coronal and $n = 3$ mice for sagittal sections; one-way ANOVA followed by Dunnett's multiple comparison).

recorded simultaneously and always displayed higher efficacy in RAD than in OR, as known from depth profiles obtained during electrode implantation in vivo (Kaibara and Leung 1993; Leung and Péloquin 2010; Shires et al. 2012; Gruart et al. 2015). Histological analyses provided assurance about the location of tip of each electrode.

### *Stronger LTP in Basal than in Apical Synapses of CA1 Pyramidal Cells*

Here, in freely moving mice, HFS induced stronger LTP in basal dendrites (OR) than in apical dendrites (RAD), consistent with results obtained in freely moving rats (Leung and Shen 1995) and in rat slices with intact synaptic inhibition (Arai et al. 1994; Haley et al. 1996; Sajikumar et al. 2007). Intact inhibition is likely to contribute to the OR/RAD difference in LTP magnitude in rodents, since basal CA1 dendrites of freely moving rats are less inhibited than apical dendrites (Kaibara and Leung 1993). Indeed, more interneurons in CA1 project to the apical than to the basal dendrites (Klausberger and Somogyi 2008). The lower threshold to induce LTP in basal (than in apical) CA1 dendrites (Leung and Shen 1995) could also be caused by basal dendrites either being more efficient to integrate synaptic excitation to generate an action potential (Øivind Hvalby, personal communication) or being more easily modifiable than apical dendrites as observed for neocortical pyramidal neurons (Nevian et al. 2007), e.g., because of the low density of HCN channels in basal CA1 dendrites (Lörincz et al. 2002). Other factors contributing to generate stronger LTP in OR than in RAD could be distinct cellular mechanisms, e.g., involving distinct isoforms of nitric oxide (Haley et al. 1996), voltage-gated calcium channels or brain-derived neurotrophic factor (BDNF) (Navakkode et al. 2012). Based on our results, D4Rs may also contribute to set the LTP threshold in OR distinct from RAD. Distinct LTP thresholds in basal and apical dendrites play an important role for the associativity between these distinct dendritic compartments as demonstrated for synaptic tagging during LTP (Alarcon et al. 2006; Sajikumar and Korte 2011). Finally, the reduced PPR that we observed to persist following LTP induction up to four hours in both OR and RAD indicates presynaptic mechanisms are involved in hippocampal LTP expression, consistent with earlier work (Schulz et al. 1994; Madroñal et al. 2009).

### *D4R Agonist Modulates Synaptic Transmission Stronger in Basal than in Apical Dendrites*

In freely moving rats, D2-like DAR agonists intraventricularly injected at high concentrations reduce basal synaptic transmission in perforant path-dentate gyrus granule cell synapses, whereas lower concentrations have receptor priming effects regulating synaptic plasticity (Manahan-Vaughan and Kulla 2003). Similarly, regarding D4Rs and observations in slices, the D4R agonist PD at µM concentrations (e.g., 20–40 µM) reduces AMPA responses in PFC pyramidal neurons and interneurons (Yuen and Yan 2009; Yuen et al. 2010), whereas PD at nM concentrations (e.g., 100 nM) has no effect during basal synaptic transmission (e.g., before LTP induction) on synaptic AMPA responses or AMPAR internalization in hippocampal neurons (Kwon et al. 2008; Herwerth et al. 2012), including fast-spiking interneurons (Andersson, Johnston, Fisahn et al. 2012). Consistently, here in freely moving mice, a lower dose

of PD (2.5 mg/kg) had no effect on basal synaptic transmission both in OR and RAD of CA1, whereas a higher dose of PD (10 mg/kg) reduced basal synaptic transmission, which was more pronounced in OR than in RAD as observed for slope and PPR of evoked LFPs. Thus, only the lower dose of PD allowed the investigation of receptor priming effects, e.g., modulating LTP (see below). As DA activates D2-like DARs under tonic stimulation by ambient low levels of DA and D1-like DARs upon phasic DA input, acute effects on basal synaptic transmission in the hippocampus are likely dominated by D2-like DA receptors including D4Rs. Consistently, D1/5R agonists have no immediate effect on basal AMPAR-mediated transmission neither in slices (Otmakhova and Lisman 1996; Mockett et al. 2004; Herwerth et al. 2012) nor in freely moving rats (Lemon and Manahan-Vaughan 2006, 2012). Due to our intraperitoneal injections, the reservation must be made that extrahippocampal effects cannot be excluded. Still, we injected PD intentionally, since systemic administrations of PD have been shown to improve memory performance in high concentrations (Bernaerts and Tirelli 2003; Sood et al. 2011).

### *D4R Agonist Modulates LTP in Basal Dendrites Distinctly from Apical Dendrites*

In the presence of the D4R agonist PD, we observed reduced LTP in OR but not in RAD in single CA1 neurons (Herwerth et al. 2012). Here in freely moving mice, we confirmed this pathway specificity. A low dose of PD (2.5 mg/kg) reduced LTP in OR but not in RAD. Furthermore, a higher dose of PD (10 mg/kg) additionally and exclusively reduced early phase LTP in OR, which is explained by the fact that this high dose reduced basal synaptic transmission. Yet, the low dose of PD was sufficient to induce receptor priming effects in basal dendrites, since the high dose of PD reduced late phase LTP in OR to an extent similar to the low dose. The reduction of late phase LTP in RAD with the high dose of PD developed gradually over 3–4 h and was therefore not observed during our shorter lasting whole-cell recordings in slices (Herwerth et al. 2012). In contrast, the LTP reduction in OR was maximal already 2 h after induction, again indicating that apical dendrites are less sensitive to D4R agonist treatment than basal dendrites.

The fast PD effect on early phase LTP in OR in vivo is consistent with our observations in vitro (Herwerth et al. 2012), which suggested a G protein-independent, calcium-dependent reduction of NMDA receptor activity. Similar fast reductions of NMDAR currents were obtained in prefrontal and hippocampal pyramidal neurons via D2-like receptor agonists including PD, involving protein kinase A as well as receptor tyrosine kinases (Kotecha et al. 2002; Wang et al. 2003).

The slower action of PD to reduce LTP in RAD (compared with OR) could be the consequence of pathway-specific induction and/or expression of LTP (see above) and/or mechanisms of PD action are different in OR vs. RAD. D4Rs belong to the D2-type DA receptors which are negatively coupled to the formation of cAMP by inhibiting adenylyl cyclase (Missale et al. 1998; Beaulieu and Gainetdinov 2011). Therefore, PD-mediated cAMP-dependent mechanisms could contribute to reduce LTP, since PKA gates hippocampal early LTP in slices (Otmakhova and Lisman 1996) and in vivo (Lemon and Manahan-Vaughan 2006). In addition, it will be interesting to find out whether D4R activation will also be involved in depotentiation of LTP in vivo as observed in apical dendritic synapses in vitro (Kwon et al. 2008).

A differential modulation of synaptic plasticity in basal and apical dendrites appears not to be restricted to DAR subtypes, since mGlu5 receptor activation selectively modulates late LTP in apical dendrites, whereas mGluR1 receptor activation modulates late LTP both in basal and apical dendrites (Fan 2013).

### *D4R Activation Before LTP Induction Prevented a Persistent PPR Reduction*

During basal synaptic transmission in OR and RAD, PD transiently reduced evoked LFPs and concurrently increased PPRs, suggesting involvement of presynaptic mechanisms, likely decreasing transmitter release. Immediately after LTP induction in the presence of PD, the PPR decrease caused by LTP induction alone combined with the PPR increase caused by PD injection alone. Once the transient effect on PPR caused by PD alone was over, likely postsynaptic mechanisms contributed to reduce LTP, since PD at both concentrations reduced LTP in OR, although PPR was still reduced (see around 120 min in Fig. 3*C*). During the fourth hour after induction, the persistent decrease in PPR after LTP induction as observed in NS was no longer detected and correlated with a significantly reduced LTP. Thus, D4R activation before LTP induction prevented a persistent PPR reduction.

### *VTA/SN Dopaminergic Afferents Within Hippocampal Area CA1*

Antibody staining against mCherry indicated that the density of dopaminergic axons, originating from VTA/SN was highest in SLM and comparable in OR and RAD. Based on these results, the distribution of VTA/SN dopaminergic fibers on its own cannot account for the differential PD modulation of synaptic efficacy in the dorsal hippocampus that we describe here. On the other hand, DA released via reversed transport of norepinephrine is likely an alternative source of DA in area CA1 (Smith and Greene 2012). Although it is unknown whether adrenergic fibers innervate area CA1 differentially, CA1 subregions show different expression pattern of $\beta_1$ and $\beta_2$ receptors that could contribute to a differential modulation of synaptic efficacy via monoamines (Booze et al. 1993).

D4R expression is homogeneous in OR and RAD (Khan et al. 1998) and appears to be largely expressed in GABAergic, fast-spiking interneurons (Andersson, Johnston, Herman et al. 2012). In acute slices, D4Rs mediate an NMDAR-dependent increase in kainate-induced gamma oscillations whose mechanism is not fully understood (Andersson, Johnston, Fisahn et al. 2012). When synaptic inhibiton is blocked, PD reduced NMDA currents in basal but not in apical dendrites of CA1 neurons (Herwerth et al. 2012). We therefore consider distinct interactions of D4R with other membrane proteins including NMDARs and AMPARs or signaling networks (e.g., neuregulin-ErbB-PI3 kinase) to be responsible for the differential OR/RAD modulation of glutamatergic transmission.

### *Possible Functional Implications*

Our results in vivo with the D4R agonist indicate that DA more strongly modulates basal than apical dendrites in area CA1, which appears to be opposite from cholinergic modulation as the cholinergic agonist carbachol attenuated excitatory postsynaptic potentials stronger in apical than in basal dendrites (Leung and Péloquin 2010). A requirement for differential modulation of hippocampal inputs is conceivable, since the hippocampus

is thought to compare expected (learned) and experienced (current) information concerning spatial and contextual features, and mismatches detected by prediction errors are valued by the midbrain DA system (Lisman and Otmakhova 2001; Mizumori and Jo 2013).

### Authors' Contributions

S.-B.L. and G.K. conceived and designed research; S.-B.L. performed and analyzed electrophysiological and histological experiments; D.D. performed and analyzed immunohistochemical experiments; M.T.H generated viruses; S.-B.L. drafted the manuscript; S.-B.L. and G.K. wrote the manuscript; all authors revised and approved the final version of the manuscript.


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