Adult neurogenesis, a particular form of plasticity in the adult brain, is under dynamic control of neuronal activity mediated by various neurotransmitters. Despite accumulating evidence suggesting that the neurotransmitter dopamine (DA) regulates proliferation of neural precursor cells in the neurogenic zones, whether and how it acts on newly generated neurons that integrate into the established network remains unknown. Using patch-clamp recordings from retrovirus-labeled newborn hippocampal dentate granule cells (DGCs) in acute mouse brain slices, we found that DA not only caused a long-lasting attenuation of medial perforant path (MPP) inputs to the young DGCs, but also decreased their capacity to express long-term potentiation (LTP). In contrast, DA suppressed MPP transmission to mature DGCs to a similar extent but did not influence their LTP expression. This difference was linked to activation of distinct subtypes of DA receptors (D1-like receptors). Although DA had a general inhibitory effect on synaptic transmission to mature DGCs as well, it exerted its impact of DA on entorhinal excitatory input to DGCs at discrete developmental stages. We observed a critical period when both DA and its receptor expression to adult-born DGCs were downregulated by activation of D1-like receptors. Despite emerging studies revealing the role of DA in the early phases of adult neurogenesis, dopaminergic regulation of functional integration of nascent neurons has yet to be determined. This lack of available data prompted us to investigate whether DA influences newborn DGCs differently than their older counterparts.

By labeling and birthdating newly generated DGCs in adult mice, we used whole-cell patch-clamp approaches to examine the impact of DA on entorhinal excitatory input to DGCs at discrete developmental stages. We observed a critical period when both the efficacy and LTP of medial perforant path (MPP) transmission to adult-born DGCs were downregulated by activation of D1-like receptors. Although DA had a general inhibitory effect on synaptic transmission to mature DGCs as well, it exerted its action via D1-like receptors and did not influence LTP in mature cells. Together, our results suggest that the responses of adult-born neurons to DA vary with developmental periods, and this differential regulation by neuromodulators poten-
tially affects the contributions of young neurons to the func-
tion of the entire DG.

Materials and Methods

Retrovirus injection. Human embryonic kidney 293T (HEK293T) cells were transfected with murine Moloney leukemia virus-based retroviral vector encoding green fluorescent protein (GFP), and the viruses were harvested from infected cultures as previously described (Zhao et al., 2006). The concentrated viral solution (10^7–10^8 colony-forming units/ml) was delivered to the DG of the mouse hippocampus through stereotaxic surgery to label dividing NPCs and their progeny. The injection site was determined using spatial coordinates relative to bregma, where d represents the distance between bregma and lambda, as follows: antero-posterior = −d/2 mm; lateral = −1.6 (if d ≥ 1.6 mm) or −1.7 mm; and ventral = −1.9 mm (from dura). The mice used for injection were female C57BL/6 and were 6–7 weeks old at the time of surgery. They were then housed in standard cages before any further experimentation. All experi-
mental procedures were approved by the Salk Institutional Animal Care and Use Committee.

Immunohistochemistry and microscopy. The retrovirus-infected mice were anesthetized with a mixture of ketamine/xylazine (100 mg/kg and 10 mg/kg, respectively) and perfused transcardially with 0.9% saline fol-
lowed by 4% paraformaldehyde. After decapitation, the mouse brains were fixed with 4% paraformaldehyde and equilibrated in 30% sucrose. Coronal slices of 40 μm thickness were cut with a sliding microtome. A polyclonal anti-mouse tyrosine hydroxylase (TH) antibody (1:250 dilution; Protos Biotech) and a monoclonal anti-mouse NeuN antibody (1:250 dilution against the primary anti-TH and anti-NeuN antibodies, respec-
tively; a secondary antibody (1:250 dilution; Jackson ImmunoResearch) were used against the primary anti-TH and anti-NeuN antibodies, respec-
tively. Biotin-labeled antibodies were then detected using streptavidin
coupled to Cy3 (1:250 dilution; Jackson ImmunoResearch). Immuno-
stained tissue samples were mounted on glass slides, and fluorescence images were obtained using a Zeiss LSM 710 laser scanning confocal
microscope. Image stacks were collected with a 20X objective lens at a
digital zoom of 4 and were compressed into a single plane by using a
maximum intensity projection and ZEN software.

Quantitative real-time PCR of DA receptor mRNA. Female C57BL/6 mice (10 weeks old) housed under standard conditions were used in this study. The DG, CA1, and CA3 of the hippocampus and striatum were microdissected from the fresh mouse brains as described before (Zhao et al., 2001) and frozen separately at −80°C in RNA-Beam reagent (Tel-Test) immediately. Tissues from five mice were pooled in one group to increase the quantity of RNA and to minimize animal-to-animal variation. For better quantification, three groups of animals were dissected and pro-
cessed independently using identical procedures. For extraction of total
RNA, the tissues were homogenized in RNA-Beam reagent, and the
homogenate was separated into aqueous and organic phases as described by the manufacturer. The pure RNA was obtained from the aqueous phase by isopropanol precipitation, and the pellet was dissolved in 10 μl of
dEPC (diethylpyrocarbonate)-treated sterile distilled water. Quantita-
tion of RNA obtained from these samples was performed with a Nano-
Drop ND-1000 Spectrophotometer. For each quantitative PCR (qPCR) reaction, 2 μg of total RNA was used, and the mRNA was first reverse transcribed into cDNA using SuperScript III reverse transcriptase (RT) (Invitrogen). Aliquots of cDNA and primers were then added to SYBR
Green Master Mix (Applied Biosystems). PCR amplifications were run
on 96-well optical reaction plates using an ABI Prism 7000 sequence
detection system, and data analysis was performed with SDS 2.3 software
(Applied Biosystems). Each condition was acquired in triplicate. Primer pairs for all five subtypes of DA receptors were designed using Primer
Express Software (Applied Biosystems). Total RNA extracted from
mouse whole brain was used to generate a standard curve by qPCR for
every gene, and the efficiency of each primer pair was verified by linear
regression to the standard curve. Serial dilutions of total RNA from
whole brain were used as standards to quantify mRNA levels of the
housekeeping gene glyceraldehyde-3-phosphate dehydrogenase
(GAPDH). The amount of each subtype of DA receptor mRNA was
calculated according to the standard curve for its particular primer set.
The relative expression level of each receptor was then normalized to that of GAPDH mRNA. Sequences of the primers used for qPCR are listed in the order of 5’ → 3’ in Table 1.

Electrophysiology. The mice injected with retrovirus expressing GFP were anesthetized by isoflurane inhalation after being housed in standard cages for different periods of time. The brains were immediately removed and placed in ice-cold artificial CSF (ACSF) containing the following (in mM): choline chloride 110, KCl 2.5, NaH2PO4 1.3, NaHCO3 25.0, CaCl2, 0.5, MgCl2, 7, glucose 20, Na-aspartate 1.3, and Na-pyruvate 0.6. Horiz-
ontal slices (25 μm thick) were cut with a Leica VT1000S vibratome and
incubated in standard ACSF composed of the following (in mM): NaCl 125, KCl 2.5, NaH2PO4, 1.3, NaHCO3 25, CaCl2, MgCl2, 1.3, Na-aspartate 1.3, Na-pyruvate 0.6, and glucose 10, saturated with 95% O2 and 5% CO2. After recovery at room temperature for at least 1 h, the slices were transferred to the recording chamber. Whole-cell perfomed patch recordings were obtained from DGCs visualized using an upright microscope (BX51WI; Olympus) with infrared differential interference contrast optics. The newborn cells were visually identified by their green fluorescence as well. During each recording, the slice was constantly perfused with fresh ACSF containing 50–100 μM picrotox to block
GABAergic synaptic transmission, and all experiments were performed at room temperature. The micropipettes were made from borosilicate
glass capillaries (Garner), with a resistance in the range of 3–6 MΩ.

The pipette was tip filled with internal solution composed of the following (in mM): K-glucuronate 128, KCl 17.5, NaCl, 1.3, EGTA 0.2, and HEPES 10, pH 7.3; then back-filled with the same internal solution containing amphotericin B (200 μg/ml). A bipolar tungsten electrode was used for extracellular stimulation of MPP, and DGCs were generally held at a constant potential of ~70 mV in voltage-clamp mode unless stated oth-
wise. Data were acquired using patch-clamp amplifiers (Axopatch 200B; Molecular Devices). Signals were filtered at 2 kHz and sampled at 5
kHz using a Digidata 1322A analog–digital interface (Molecular De-
vices). Input resistance and series resistance were monitored continu-
ously during recordings. Series resistance was typically ~20 MΩ. The
mean input resistance was ~745 MΩ for newborn and ~540 MΩ for
mature DGCs. Data were accepted for analysis only if both series and
input resistances remained relatively constant (~20% change) through-
out the experiment. LTP was induced with four episodes of theta-burst
stimulation (TBS) applied at 0.1 Hz. Each episode of TBS consisted of
trains of stimuli delivered every 200 ms, with five pulses (at 100 Hz) in
each train. The extent of LTP was quantified by averaging the amplitude
of EPSCs during the last 10 min of experiments and normalizing the result to the mean baseline value. The paired-pulse ratio (PPR) was cal-
culated as the ratio of the amplitude of the second EPSC to that of the first
EPSC evoked by paired-pulse stimulation of MPP, and the coefficient
of variation (CV) was calculated as σ/μ, where σ and μ are the SD and the
mean amplitude of first EPSC, respectively. Unless indicated, data were
d compared with either Student’s t test (paired or unpaired) or Wilcoxon
signed-rank test, and results associated with p < 0.05 were considered to
be statistically significant. All the agonists and antagonists for DA recep-
tors were purchased from Tocris Bioscience and added to the external
solution as indicated. The other drugs were obtained from Sigma.

| Table 1. Sequences of the primers used for qPCR analysis |
| Gene | Sense | Anti-sense |
| D1R | GACGAGCAGACATGCCATT | AGTCTTGGACCTGAGCTCT |
| D2R | GCACAGCAGGACCTGTTAAC | AGGTCACGACGACGACGAC |
| D3R | AGCTGAGAGGAGGAAGAAC | GTGACCCAGACGACGAC |
| D4R | TTCAACCTTGGCCGATTC | CATCAGGACGACGAC |
| GAPDH | ACCGAAAAGCTCTGATGGG | CCATCGGTTGAGGAC |

D1R, D2 receptor; D2R, D3 receptor; D3R, D4 receptor; D4R, D5 receptor; GAPDH, D5 receptor.
immunopositive puncta of relatively higher intensity were readily varied from weak to moderate throughout the dentate area. Small cells were found in a diffuse and sparse pattern, and the staining intensity from essentially all samples tested.

1.5–1.75 cells were used for each PCR. GAPDH could be detected reliably (sequences the same as those used for qPCR). Therefore, cDNAs of only showing in Figure 1, marker NeuN was included to visualize the granule cell layer. As enzyme in DA synthesis, and immunoreactivity for pan-neuronal markers, the hippocampal dopaminergic neurons are observed in the DG (tem de la Rie et al., 1998). To ascertain the ability of endogenous DA to modulate MPP-elicted responses, as evidenced by their different sensitivity to mGluR (metabotropic glutamate receptor) agonists, AP4 and GABA_A agonist baclofen (supplemental Fig. S1, available at www.jneurosci.org as supplemental material). After a 10 min stable baseline of evoked EPSCs was achieved, DA (10–20 μM) was applied through bath perfusion for 5 min, which decreased the EPSC amplitude by 26.2 ± 6.5% and 30.9 ± 4.6%, respectively, in GFP+ (n = 8) and GFP− (n = 15) DG cells (30–40 min). In contrast, there was no significant reduction in EPSCs in time-matched saline controls (GFP+: 1.8 ± 6.8%, n = 4; GFP−: 4.5 ± 5.5%, n = 5) (Fig. 2A). DA-induced inhibition developed slowly and was long lasting. It persisted as long as the recording remained stable (up to 95 min after washout of DA), indicating that DA induced a novel form of long-term depression (LTD) in the DG.

To ascertain the ability of endogenous DA to modulate MPP inputs to DGCs, we next investigated the action of amphetamine into a sterile 0.5 ml PCR tube (Bio-Rad). The RNA was converted to cDNA through reverse transcription (SuperscriptIII; Invitrogen). About one quarter of the final RT sample was subsequently analyzed by two rounds of PCR amplification (GoTaq flexi; Promega) using specific primers for D_1, D_2, and D_3 receptors and housekeeping gene GAPDH (sequences the same as those used for qPCR). Therefore, cDNAs of only 1.5–1.75 cells were used for each PCR. GAPDH could be detected reliably from essentially all samples tested.

**Results**

**Differential regulation of newborn and mature DGCs by DA**

The major terminal fields of dopaminergic projections to the hippocampal formation are located in the ventral/dorsal subiculum and CA1 (Gasbarri et al., 1997). Few afferents to adult-born DGCs, we injected 6- to 7-week-old mice with retrovirus carrying GFP transgene by stereotaxic surgery to label and birthdate newly generated granule cells. The mice were killed at different time points after retroviral injection. The brain sections were immunostained for TH, the rate-limiting enzyme in DA synthesis, and immunoreactivity for pan-neuronal marker NeuN was included to visualize the granule cell layer. As shown in Figure 1A, TH+ dopaminergic fibers were largely found in a diffuse and sparse pattern, and the staining intensity varied from weak to moderate throughout the dentate area. Small immunopositive puncta of relatively higher intensity were readily found in the SGZ, where the NPCs are located. At a higher magnification, TH+ dopaminergic fibers were found to be in the vicinity of both dendrites and somata of newborn DGCs. These results suggest that the processing of cortical inputs to the principal neurons of DG may be influenced by DA.

DA exerts its action via D_1-like (D_1 and D_2) and D_2-like (D_2, D_3, and D_4) families of receptors. Typically, these two classes of receptors lead to opposite changes in intracellular cAMP levels and trigger distinct signaling cascades that culminate in gene transcription (Missale et al., 1998). To evaluate the expression levels of DA receptors in the DG, we performed qPCR analysis of RNA extracted from microdissected adult mouse brain regions (DG, CA1, CA3, and striatum). The DA receptor measurement for each brain subregion was normalized over a simultaneously performed qPCR of the housekeeping gene GAPDH in that area. Each DA receptor subtype showed a trend of consistent expression in the DG (compared with 0, p = 0.1, Wilcoxon signed-rank test), and their expression levels were comparable to those in the striatum (Fig. 1B), a brain area that has been demonstrated to express all five DA receptor mRNAs (Missale et al., 1998). Furthermore, D_1, D_2, and D_3 receptors had higher expression levels than the other subtypes in the DG. In contrast, the D_5 receptor appeared to be the only subtype that showed marked expression in CA1 and CA3. Overall, DA receptors exhibited higher expression in the DG than in the other hippocampal subregions, indicating a particular role for DA in DG function.
(AMT), a psychostimulant that is known to actively promote DA release. As shown in Figure 2B, AMT (30 μM) decreased the amplitude of EPSCs in GFP<sup>−</sup> neurons by 22.8 ± 4.1% (n = 6). Interestingly, the same drug treatment did not cause any significant effect on EPSCs in 4 wpi GFP<sup>+</sup> neurons, but administration of AMT at a much higher concentration (60 μM) reduced their EPSC amplitudes by 35.9 ± 4.9% (n = 5). Preincubation of the brain slices in D<sub>1</sub>-like receptor antagonist SCH 23390 (10 μM), but not D<sub>2</sub>-like receptor antagonist sulpiride (10 μM), for at least 30 min before infusion of AMT largely abolished the synaptic changes in GFP<sup>+</sup> cells. In contrast, the same pretreatment with sulpiride, but not SCH 23390, prevented the depressive effect of AMT on GFP<sup>−</sup> neurons (Fig. 2B). These results suggest that endogenous DA releasable by AMT suppressed MPP inputs to both adult- and neonate-born DGCs through D<sub>1</sub>-like receptor subtypes, respectively. Furthermore, the need for a higher concentration of AMT in newborn neurons might be attributed to a lower AMT-induced synaptic DA level resulting from fewer dopaminergic synapses on young cells and/or lower efficacy of the corresponding synapses.

DA is an important modulator of LTP at glutamatergic synapses throughout the brain (Jay, 2003; Lisman and Grace, 2005). Most studies in the hippocampus have focused on its role in the CA1 area and during tetanization, which produces LTP. Here we sought to understand whether DA could leave a trace in the learning ability after its removal (i.e., whether it could induce lasting changes that regulate how synapses respond to subsequent induction of LTP). To address this issue, we compared the magnitudes of LTP induced before and after exposure to DA. In naïve control slices, evoked EPSCs could be reliably potentiated by TBS in both GFP<sup>+</sup> (n = 11) and GFP<sup>−</sup> (n = 16) neurons. Consistent with previous findings (Snyder et al., 2001; Ge et al., 2007), the average enhancement level of EPSCs in GFP<sup>+</sup> DGCs was significantly higher than that in mature GFP<sup>−</sup> cells. In contrast, when the TBS protocol was applied 50 min after DA application, the mean magnitude of LTP in GFP<sup>−</sup> DGCs (n = 6) was not changed, whereas that in GFP<sup>+</sup> DGCs (n = 5) was dramatically decreased (Fig. 2C). Thus, DA exclusively reduced the capacity of MPP synapses on immature adult-generated DGCs to undergo plastic changes. This finding suggests that the DG may encode information differently before and after events that stimulate DA release. Induction of LTP by high-frequency stimulation is predominantly mediated by activation of NMDA receptors (Nicoll and Malenka, 1999). We thus speculated that DA modulated synaptic plasticity of newborn neurons by modification of NMDA receptors, and we explored the possibility by recording isolated NMDA component in Mg<sup>2+</sup>-free ACSF (4 mM Ca<sup>2+</sup>) with 10 μM CNQX and 50 μM picrotoxin. As shown in supplemental Fig. S2 (available at www.jneurosci.org as supplemental material), the amplitude of NMDA currents in 4 wpi GFP<sup>+</sup> DGCs was decreased by 21.1 ± 3.3% at 30–40 min after perfusion of DA (n = 4). Therefore, DA attenuated LTP expression in young neurons, probably by inhibiting synaptic NMDA receptor responses.

**D<sub>2</sub>-like receptor-mediated attenuation of cortical inputs to mature DGCs**

To pharmacologically characterize the subtype of receptors involved in differential modulation of entorhinal excitation by DA, we examined the actions of selective agonists of D<sub>1</sub> and D<sub>2</sub> receptor families on evoked EPSCs, respectively. The first set of recordings was performed from GFP<sup>−</sup> DGCs residing in the outermost granule cell layer, which is predominantly occupied by neurons born during early development (Wang et al., 2000). EPSCs were evoked by low-frequency (once every 20 or 30 s) paired-pulse stimulation (interpulse interval, 50 ms) of MMP. After stable baseline measurements of EPSCs for at least 10 min, DA receptor agonists were bath applied for 5 min, followed by a washout period of 40 min. As shown in Figure 3A, the amplitude of the first EPSC in response to paired-pulse stimulation remained unchanged after bath application of 10 μM D<sub>1</sub>-like receptor agonist SKF 38393 (n = 8). In contrast, treatment with 10 μM quinpirole, a selective D<sub>2</sub>-like receptor agonist, decreased the EPSC amplitudes by 28.9 ± 4.7% (n = 12) (Fig. 3B). These results suggest...
To clarify the locus of this depression, we compared the PPR and CV of EPSCs before and after drug application. These two measures are correlated with presynaptic release probability and therefore sensitive to manipulations altering it (Zucker and Regehr, 2002). The attenuation of evoked EPSCs resulting from quinpirole application was accompanied by a significant increase in both PPR (baseline: 0.87 ± 0.10; 30–40 min after quinpirole: 1.00 ± 0.11; p < 0.001, Wilcoxon signed-rank test) (Fig. 3C) and CV (baseline: 0.16 ± 0.02; 30–40 min after quinpirole: 0.22 ± 0.02; p < 0.05) (Fig. 3D). Thus, D2-like receptor-mediated suppression of evoked EPSCs appeared to act at least partially through inhibition of presynaptic release of glutamate, although the contributions of additional postsynaptic mechanisms could not be ruled out.

D2-like receptor-mediated attenuation of cortical inputs to immature DGCs

We next used the same experimental design as described in Figure 3 to investigate receptors involved in DA regulation of MPP inputs to GFP+ DGCs at 4–6 wpi, when most newborn cells have already integrated into the existing circuitry but have not yet fully matured morphologically or functionally (Espósito et al., 2005; Zhao et al., 2006). In contrast to the effect on MPP inputs to mature DGCs, bath-applied quinpirole did not cause any significant alteration in excitatory synaptic transmission at MPP–newborn DGC synapses, as shown by no changes in the amplitudes of the EPSCs in response to paired-pulse MPP stimulation after drug perfusion (n = 8) (Fig. 4A). Instead, the amplitude of the first EPSC was decreased to 71.7 ± 5.6% (n = 9) by bath application of SKF 38393, which was not associated with significant changes in PPR (baseline: 0.96 ± 0.10; after SKF 38393: 0.99 ± 0.15) or CV (baseline: 0.19 ± 0.02; after SKF 38393: 0.20 ± 0.02) (Fig. 4B). These results suggest that the attenuation of MPP inputs to newborn DGCs was mediated by D2-like receptors and seemed unlikely to involve a decrease in presynaptic release of glutamate. However, more direct evidence is needed to confirm its postsynaptic origin.

Applying the same experimental paradigm to GFP+ DGCs at 8–11 wpi, we then examined whether adult-born DGCs maintained this property after they became morphologically and physiologically mature. Bath perfusion of quinpirole (n = 14) instead of SKF 38393 (n = 8) resulted in 25.1 ± 6.9% decrease of the first EPSC evoked by paired-pulse stimulation of MPP (Fig. 4C), and this synaptic depression was accompanied by an increase in both PPR (baseline: 0.77 ± 0.06; after quinpirole: 0.91 ± 0.09; p < 0.005, Wilcoxon signed-rank test) and CV (baseline: 0.16 ± 0.01; after quinpirole: 0.21 ± 0.02; p < 0.001) (Fig. 4D). Preincubation of the brain slices in SCH 23390 and sulpiride separately for at least 30 min before
bath perfusion of the corresponding agonist completely prevented the changes in EPSC amplitude, confirming that the depressive effect of SKF 38393 and quinpirole was specifically mediated by D₁- and D₂-like receptors, respectively (Fig. 4E). It should be noted that application of either D₁ or D₂ antagonist on its own did not elicit significant alterations in basal synaptic transmission, suggesting that a tonic activation of D₁- or D₂-like receptors did not contribute to basal synaptic transmission in DG. Together, our observations demonstrate that DA modulated synaptic responses of DGCs born during adulthood and during early development through activation of distinct subtypes of DA receptors, which then involved different synaptic mechanisms. Furthermore, the activated DA receptors shifted from a D₁- to a D₂-like family during maturation of adult-born DGCs.

Mechanisms underlying DA receptor-mediated depression

The above results indicate that DA may induce a novel form of LTD via D₁- or D₂-like receptor-dependent signaling in the DG. LTD in this region can also be induced both in vitro and in vivo by a variety of electrical stimulus protocols, the most common of which is low-frequency (1–2 Hz) stimulation (LFS) of MPP (Abraham, 1996). Accumulating evidence has shown that LFS-induced LTD-like processes contribute to hippocampal information storage, which is essential for learning and memory (Bear and Abraham, 1996; Kemp and Manahan-Vaughan, 2007). If DA-LTD and LFS-LTD use a common mechanism for expression, generation of either one of them should occlude the other. To test this possibility, in the first experiment we delivered LFS (900 pulses at 1 Hz) to MPP after minimal 10 min stable baseline recordings of evoked EPSCs in three groups of DGCs of different ages (4 wpi: GFP⁺; 4–5 wpi, 8 wpi: GFP⁺; 8–9 wpi: mature, GFP⁺). The normalized EPSC amplitudes 20–30 min after LTD induction were 70.0 ± 8.4% (4 wpi: n = 5), 67.9 ± 11.4% (8 wpi: n = 4), and 68.7 ± 3.7% (mature: n = 6) of baseline (Fig. 5A). In the same brain slices, subsequent treatment with either D₁- or D₂-like receptor agonist could not induce a further decline in the synaptic transmission (4 wpi: 103.5 ± 1.7% of the baseline recorded in the last 10 min before drug perfusion; 8 wpi: 86.0 ± 11.4%; mature: 96.9 ± 5.8%). These results indicate that D₁- or D₂-LTD was occluded by prior induction of LFS-LTD. We next performed a reverse occlusion experiment in which LFS was delivered after DA receptor agonists were applied and the amplitude of EPSC had steadily declined to reach a plateau (~40–50 min after drug application). Under this condition, LFS still induced LTD in all three groups of cells (Fig. 5A).

Compared with baselines recorded in the last 10 min before LFS, the normalized EPSC amplitudes 20–30 min after the end of LFS were 64.4 ± 3.7% (4 wpi: n = 6), 75.1 ± 3.7% (8 wpi: n = 4), and 79.4 ± 5% (mature: n = 6). The magnitudes of LFS-LTD after SKF 38393 or quinpirole treatment were not significantly different from those of LFS-LTD elicited in naive slices (Fig. 5B). In sum, induction of LFS-LTD fully blocked subsequent depression caused by D₁- or D₂-like receptor agonists, but not vice versa, suggesting that the intracellular signaling mechanisms underlying DA receptor-mediated LTD do not fit exactly with LFS-LTD. One possibility is that LFS-LTD recruits both D₁- and D₂-dependent components; therefore, LFS-LTD occludes either of them, whereas neither alone occludes LFS-LTD. Further investigation of whether LFS-LTD depends on D₁- and D₂-like receptors could be undertaken to test this hypothesis.
D1- and D2-like receptors are classically known to couple to G-proteins that regulate adenylyl cyclase (AC)-catalyzed cAMP formation, which then activates protein kinase A-dependent signaling cascades (Greengard, 2001). There is also evidence that both families may couple to phospholipase C (PLC)-mediated mobilization of intracellular Ca2+. (Neve et al., 2004). Downstream, through diverse cAMP- or Ca2+-dependent mechanisms, DA influences synaptic transmission and plasticity by modulating the activity of various ion channels, receptors, and transcription factors. We first examined the participation of AC, whose activation regulates the production of cAMP. Since AC inhibitor SQ 22536 (100 μM) inhibited baseline synaptic transmission on its own and the depression reached a plateau level within 40–50 min after drug infusion (supplemental Fig. S4A, available at www.jneurosci.org as supplemental material), the slices were preincubated with SQ 22536 for >1 h before new baseline recordings were acquired. The drug was then present in the superfusing medium throughout every recording. SKF 38393 added after AC inhibitor treatment still reduced the evoked EPSCs in 4–5 wpi GFP+ neurons to 82.5 ± 7.3% of the new baseline values. Although the progression of D1 receptor-mediated suppression appeared to be slowed down by AC inhibition, the final magnitude of depression was comparable to that caused by SKF 38393 alone (Fig. 6A). In contrast, inhibition of AC by SQ 22536 largely abolished quinpirole-induced reduction of evoked EPSCs in GFP+ neurons (Fig. 6B). These findings suggest that the AC/cAMP pathway contributed to D2-LTD in mature DGCs but not D1-LTD in young newborn cells. In diverse brain areas, D2 receptor activation has been shown to inhibit AC and subsequent cAMP formation (Missale et al., 1998). If this was the mechanism underlying D2-LTD, forskolin, a membrane-permeable direct activator of AC, would be expected to raise cAMP levels and cause potentiation of EPSCs evoked by MPP stimulation. Indeed, bath application of forskolin (10 μM) for 5 min produced a rapid and pronounced enhancement of the EPSC amplitude in neonate-
generated DGCs (110.4 ± 7.4%, n = 6) (Fig. 6B), although it appeared to reverse faster on washout than D2-LTD. Together, these findings suggest that preblockade of AC by SQ 22536 occluded D2 agonist-induced depression. Thus, activation of D2-like receptors in the DG appeared to decrease intracellular cAMP accumulation by inhibiting AC.

Forskolin produced an even stronger potentiation of EPSCs in 4 wpi adult-generated DGCs (137.8 ± 11.7%, n = 5) (Fig. 6A), which implies that D2-like receptors were either not expressed or not coupled to the AC/cAMP pathway in young neurons. To test the first possibility, we used a DGC-specific RT-PCR technique to analyze RNA transcript levels in individual newborn and mature DGCs. Since our qPCR data (Fig. 1B) indicated that D1, D2, and D3 receptors appeared to be the major subtypes of DA receptors expressed in the DG, we focused on comparing the levels of the three subtypes in neurons born during early development (GFP−) versus those born during adulthood (GFP+). In summary, we observed amplification of D1/D5 receptors from both GFP+ and GFP− cells (Fig. 6C, Table 2). Expression of D2 receptors was found in >5-week-old GFP+ and GFP− cells but not in 4-week-old GFP− cells (Fisher’s exact probability test, p = 0.1). Due to the intrinsic low-level expression of DA receptors and limited amount of RNA obtained by this method, the success rate of detecting DA receptor mRNAs varied. Thus, we could neither conclude that D2 receptors were absolutely absent in young DGCs nor compare the relative abundance of D2 receptors during cell maturation (5-week-old GFP+ vs 8-week-old GFP+ vs GFP−). However, these results clearly suggest that D2-like (D1 and D3) receptors were expressed in both mature (8-week-old GFP+ and GFP−) and immature DGCs, whereas D2 receptors were more easily detected in mature neurons but were undetectable from 16 RT-PCRs of young cells.

To determine whether D1- and D2-LTD involve PLC activation or Ca2+−dependent intracellular signaling processes, we then separately tested the effects of SKF 38393 and quinpirole in the presence of a PLC inhibitor, U73122 (10 μM), or a Ca2+ chelator, BAPTA-AM (10 μM). BAPTA-AM treatment alone induced a gradual decrease of synaptic transmission, indicating a strong Ca2+−chelation. The reduction of EPSC amplitude generally reached a steady state ~40 min after drug application (supplemental Fig. S4B, available at www.jneurosci.org as supplemental material). Thus, we compared the EPSC amplitudes obtained after administration of those new stable baselines acquired after the slices were perfused with the drug for ~1 h. Constant perfusion of U73122 failed to significantly block DA receptor stimulation-induced depression (Fig. 6D). Under this condition, activation by SKF 38393 of D1-like receptors in newborn neurons was still able to suppress the evoked EPSCs (SKF 38393 vs SKF 38393 + U-73122: 71.7 ± 5.6% vs 72.0 ± 6.6%; p = 0.98, t test). Likewise, activation by quinpirole of D1-like receptors in mature DGCs decreased the amplitude of EPSCs to 73.0 ± 8.0% (n = 7) in the presence of U73122. By contrast, pretreatment of brain slices with BAPTA-AM largely abolished D1-LTD in 4 wpi GFP+ DGCs (93.9 ± 8.3%, n = 5). The magnitude of D2-LTD in GFP− DGCs was also markedly reduced (quinpirole + BAPTA-AM vs quinpirole: 87.9 ± 2.7% vs 70.7 ± 5.3%; p < 0.05, t test), even though quinpirole still caused a statistically significant reduction of evoked EPSCs in the presence of BAPTA-AM. These results indicate that Ca2+−chelation blocked or occluded the effects of DA agonists. The changes in presynaptic and/or postsynaptic intracellular Ca2+, independent of PLC activation, played an essential role in depression mediated by both families of DA receptors.

Prior studies have also reported that the actions of D1/D2 receptor agonists require NMDA receptor-mediated synaptic transmission (Smith et al., 2005), and we consistently observed NMDA receptor-mediated currents under our recording condition, albeit of small amplitudes (supplemental Fig. S5, available at www.jneurosci.org as supplemental material). We therefore investigated the dependency of D1/D2-LTD on NMDA receptors by applying the agonists in the presence of the competitive NMDA receptor antagonist D-AP5 (25 μM). As shown in Figure 6D, blockade of NMDA receptor activation completely abolished the depression induced by SKF 38393 in GFP+ cells (102 ± 8.7% of baseline). However, in GFP− neurons, the mean amplitude of evoked EPSCs measured between 30 and 40 min following bath application of quinpirole in the presence of D-AP5 was 75.1 ± 4.2% of the control level (n = 9), which was comparable to that obtained in the absence of D-AP5. Thus, D1-like receptor-mediated depression of entorhinal inputs to newborn DGCs seemed to be dependent on synaptic activation of NMDA receptors, whereas this mechanism was not required for the D2-like receptor-mediated effect on mature neurons.

Table 2. Summary of single-cell RT-PCR experiment

| D1   | 3.5−4 weeks | >5 weeks | >8 weeks | D2   | 3.5−4 weeks | >5 weeks | >8 weeks | D3   | 3.5−4 weeks | >5 weeks | >8 weeks |
|------|-------------|----------|----------|------|-------------|----------|----------|------|-------------|----------|----------|
| 0/16 | 1/3         | 1/11     |          | 0/16 | 2/4         | 4/9      | 3/14     |
| 2/16 | 1/2         | 1/12     |          |

Numerators indicate number of successful RT-PCR amplifications, and denominators indicate total number of RT-PCR reactions for a given subtype of DA receptor.

Prior D1-LTD expression alters the magnitude of LTP in immature DGCs

To examine whether activation of distinct subtypes of DA receptors accounts for the differential modulation of LTP expression in mature and newborn neurons shown in Figure 2C, we delivered TBS to DGCs of different age groups 50 min after application of D1- or D2-like receptor agonists, when the EPSC amplitude appeared to reach a plateau after drug treatment. This induction of LTP returned the EPSC amplitude to a level not significantly different from original baseline in neurons of all three different ages (4 wpi: n = 8, p = 0.20; 8 wpi: n = 5, p = 0.49; mature: n = 6, p = 0.92; paired t test) (Fig. 7A−C), suggesting that TBS-LTP could reverse LTD mediated by both families of DA receptors. Although SKF 38393 had no detectable influence on the strength of MPP inputs to mature DGCs (Fig. 3A), we decided to investigate whether activation of D1-like receptors could modulate subsequent LTP induction in mature GFP− neurons. The experimental strategy was the same as that shown in Figure 7A, so we could compare the impact of D1 activation with that of D2 activation. In this experiment, LTP was successfully induced by TBS, and the increase in EPSC amplitude was 153.3 ± 9.5% (n = 7) after perfusion of SKF 38393 compared with 160.5 ± 10.2% (n = 16) in control conditions, a difference that was not statistically significant (p = 0.67, t test) (Fig. 7C,D). Remarkably, the mean magnitude of LTP in developing DGCs (4 wpi GFP+) obtained after SKF 38393 exposure was significantly smaller than that obtained before drug treatment. However, there was no statistical difference in the levels of LTP between the mature DGCs (including GFP− and 8 wpi GFP+) expressing D2-LTD and the drug-naïve DGCs (Fig. 7D). Together, these
results suggest that DA specifically decreased the plasticity of newborn DGCs via D1-like receptor-mediated signaling.

Discussion
Our findings demonstrate that DA exerted distinct modulatory effects on DGCs at different developmental stages through different receptor subtypes. Selective activation of D1-like receptors led to postsynaptically expressed LTD of synaptic transmission at MPP synapses on developing adult-born neurons, which required Ca\(^{2+}\) influx, possibly through NMDA channels. D1-like receptor-mediated signaling also decreased the amplitude of subsequent TBS-LTP in immature neurons. In contrast, selective activation of D2-like receptors did not influence the capacity of neonate-generated DGCs to express LTD but resulted in attenuation of basal MPP inputs to them, which appeared to involve a decrease in presynaptic release. Upon maturation, newborn neurons behaved the same as those generated in neonates in response to dopaminergic stimulation.

DA receptor expression in the DG
DA receptors are found to be relatively concentrated in the CA1 region, and dopaminergic modulation of synaptic transmission within this area relates to learning and memory (Gasbarri et al., 1996; Bach et al., 1999; Lisman and Grace, 2005). In the present study, qPCR was used to determine and compare the transcription profiles of DA family receptors in microdissected DG, CA1, and CA3 areas of adult hippocampus and also in a separate neural structure, the striatum, which exhibits an extremely dense innervation by dopaminergic axons. Prior analysis of mRNA band intensities suggests that striatal D\(_1\) and D\(_2\) receptors are expressed at high levels, whereas D\(_3\), D\(_4\), and D\(_5\) receptor mRNAs are present at very low levels (Missale et al., 1998), which is in agreement with the qPCR results presented in this report. Interestingly, although DG appeared to receive much less dopaminergic innervation (Fig. 1A), the mRNA levels of DA receptors in this area were comparable to those present in the striatum (Fig. 1B). Consistent with previous quantitative autoradiographic analysis showing that the molecular layer of DG contains approximately five times as many D\(_1\)-like receptors as the other areas of the hippocampus (Dawson et al., 1986), DA family receptors were apparently more concentrated in the DG than in the other hippocampal subfields, suggesting a critical role for DA in regulating the function of the DG. Furthermore, the qPCR data demonstrate that D\(_1\) and D\(_3\) mRNAs appeared to be the most abundant among all five DA receptors in the dentate, followed by D\(_2\) mRNAs. This finding is in agreement with our observation that D\(_1\)-like receptors were expressed in DGCs of all ages, whereas D\(_2\) receptors were preferentially detected in more mature cells but not found in 16 RT-PCRs from ∼4-week-old neurons (Table 2). Previously, it was reported that the affinity of D2 receptors for DA is several orders of magnitude greater than that of D1 receptors, which makes it possible that D2 receptors play a dominant role in mature DGCs even though they express D1-like receptors as well. In addition, this difference in expression might be one mechanism underlying our observation that a higher concentration of AMT was required for induction of DA-LTD in newborn cells than in mature ones (Fig. 2B).

All DA receptors are G-protein-coupled receptors (GPCRs). The expression levels of GPCRs are generally low in native tissues and therefore hard to detect, which is partially reflected by the high variability of PCR efficiency (Figs. 1B, 6C). However, one ligand-bound GPCR may activate multiple G-proteins, depending on the duration of activated GPCR, and the signal could be further amplified along downstream signal cascades. Maintenance of the signal is not only determined by the lifetime of the ligand–GPCR complex but also is affected by the amount and lifetime of the receptor–effector protein complex, deactivation of the activated receptor, and deactivation of effectors through intrinsic enzymatic activity, which might contribute to the long-lasting dopaminergic modulation observed in this study.

Mechanisms underlying differential D\(_1\) versus D\(_2\) receptor-mediated inhibition
Our present results demonstrate that DA selectively decreased the strength of MPP synapses on developing newborn DGCs (younger than 6 weeks of cell age) and impaired their ability to express LTD through activation of D\(_1\)-like receptors, whereas D\(_2\)-like receptors mediated depression of MPP synapses on mature adult-generated neurons (older than 8 weeks) and on those born during early development without disturbing their capacity to express LTD. D\(_1\)-LTD in new neurons appeared not to involve the AC/cAMP signaling cascade, as inhibition of AC failed to decrease the level of depression induced by SKF 38393. However, exposure to Ca\(^{2+}\) chelator or NMDA channel blocker, but not...
PLC inhibitor, largely abolished the effect of SKF 38393 through either blockade or occlusion, suggesting that D1-like receptor-mediated LTD involves NMDA receptors and Ca\(^{2+}\)-dependent mechanisms. In contrast, inhibition of the AC/cAMP pathway was a prerequisite for D2-LTD. Together with the finding that forskolin-induced potentiation (Fig. 6A, B) was accompanied by a decrease in PPR (data not shown), an increase in PPR associated with D2-LTD indicates that AC-mediated signaling initiated a retrograde signal from postsynaptic DGCs, which eventually resulted in reduction of neurotransmitter release from MPP terminals. D2 receptor activation has been found to trigger release of postsynaptic endocannabinoids, which act as retrograde messengers to suppress presynaptic glutamate release (Kreitzer, 2005), thereby mediating dopaminergic inhibition of excitatory transmission onto striatal medium spiny neurons (Yin and Lovenberg, 2006). Whether a similar retrograde signaling mechanism accounts for D2 actions in the DG remains to be further investigated. It is noteworthy that quinpirole depressed synaptic responses of mature DGCs to a significantly lesser degree in the presence of Ca\(^{2+}\)-chelator, but neither PLC-linked Ca\(^{2+}\) immobilization nor NMDA receptor-dependent Ca\(^{2+}\) influx was likely to contribute to this process. Given that D1-LTD appeared to have a postsynaptic locus, whereas D2-LTD might involve a presynaptic component (Figs. 3, 4), it is possible that the impact of DA on immature DGCs requires activation of NMDA receptors and a Ca\(^{2+}\)-driven intracellular signaling event in postsynaptic neurons. In contrast, DA influences mature DGCs through a postsynaptic D2-like receptor-linked AC/cAMP pathway and a subsequent retrograde messenger that activates a Ca\(^{2+}\)-dependent process in the presynaptic neuron and/or whose production may itself be Ca\(^{2+}\) dependent in the postsynaptic neuron. Additional studies will be needed to address this issue. In conclusion, although DA resulted in similar downregulation of cortical inputs to mature and newborn DGCs, the effects on the two different groups of cells appeared to occur via distinct mechanisms, which may also underlie differential modulation of their synaptic plasticity (Fig. 8).

Functional implications

A wealth of studies has been conducted on the regulatory role of DA in synaptic transmission and plasticity of CA1 pyramidal neurons (Huang and Kandel, 1995; Otomohva and Lisman, 1996, 1999; Matthies et al., 1997; Lemon and Manahan-Vaughan, 2006); however, the functional significance of the DA system in the DG remains elusive. The global inhibition of cortical inputs by DA revealed in this study might be crucial for optimizing signal-to-noise ratio in the DG, which is particularly important for its role as a filter for incoming sensory information.

DGCs generated in the adult hippocampus receive synaptic inputs from the entorhinal cortex and local inhibitory interneurons (van Praag et al., 2002; Overstreet Wadiche et al., 2005; Laplagne et al., 2006) and form functional synapses with interneurons and CA3 pyramidal cells (Toni et al., 2008). The integration of new neurons into the existing neural circuitry endows them with the capacity to make an impact on hippocampal function, which has been suggested by a strong correlation between adult neurogenesis and performance in hippocampus-dependent learning tasks (Shors et al., 2001; Saxe et al., 2006; Dupret et al., 2008; Imayoshi et al., 2008; Zhang et al., 2008; Clelland et al., 2009). However, it remains less clear whether and how adult-born DGCs at different developmental stages contribute to specific aspects of brain function. Immature granule cells in adult animals display distinct morphological and physiological features compared with mature ones, such as compact dendritic arbors, high excitability, and increased synaptic plasticity (Wang et al., 2000; Snyder et al., 2001; Schmidt-Hieber et al., 2004). When reaching maturity, adult-born cells become indistinguishable from newly generated ones in terms of the above properties (Laplagne et al., 2006; Zhao et al., 2006; Ge et al., 2007). One emerging view is that adult-born neurons at early stages may serve as major mediators for experience-dependent plasticity and therefore function as special units in the adult circuitry (Bruel-Jungerman et al., 2007). Our current study extends previous findings that the physiological properties of newborn granule cells differ from those of the existing population and indicates that newborn neurons undergo a developmental switch in response to DA stimulation through an alteration of the responsible receptors from the D1- to D2-like family. The underlying molecular mechanisms are likely to involve a developmental change in the expression level of DA receptors (Fig. 6C) and/or in the coupling efficiency of the receptors to their downstream effector proteins. Notably, the time window when LTP in new neurons is reduced by D1-like receptor-mediated signaling appears to be the same as the window when they exhibit high levels of synaptic and anatomical plasticity (Zhao et al., 2006; Ge et al., 2007). The differential dopaminergic modulation described here thus may provide an additional fine control of synaptic integration of adult-born neurons in response to experience. Given the critical role of the hippocampus–VTA loop in regulating the entry of behaviorally significant information into long-term memory (Lisman and Grace, 2005), these data have potential implications for the intriguing hypothesis that young neurons in the adult hippocampus may constitute a specific neuronal population and play unique roles in learning and memory.
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