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D1/D5 Dopamine Receptors Inhibit Depotentiation at CA1 Synapses via cAMP-Dependent Mechanism

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Recent work has shown that D1/D5 dopamine receptors can enhance long-term potentiation (LTP). We investigated whether D1/D5 receptors also affect depotentiation, the reversal of LTP by low-frequency stimulation. D1/D5 agonists greatly reduced depotentiation, an effect that was inhibited by a D1/D5 antagonist. The D1/D5 effect appears to be mediated by adenylyl cyclase (AC) and cAMP-dependent protein kinase (PKA), because it was mimicked by the AC activator forskolin and was inhibited by the AC and PKA inhibitors. *In vivo* studies show that dopamine is released when a reward occurs. Our results raise the possibility that the memory of events before reward might be retained selectively, because dopamine blocks their erasure.

Key words: adenylyl cyclase; β-adrenoreceptors; CA1; cAMP; cAMP-dependent protein kinase; depotentiation; D1/D5 dopamine receptors; early LTP; field EPSP; hippocampus; learning

Dopamine plays an important role in both working (Goldman-Rakic, 1995) and long-term memory. In long-term memory, dopamine is involved specifically in the mechanisms of reinforcement (Cooper, 1991; Schultz et al., 1993). Midbrain dopaminergic neurons respond to a reward and deliver dopamine to target brain structures, including the hippocampus (Gasbarri et al., 1994). The pivotal role of the hippocampal dopaminergic system has been demonstrated in several types of learning: intrahippocampal injections of dopamine agonists enhance passive avoidance (Bernabeu et al., 1997), visual discrimination (Grecksch and Matthies, 1982), and win–shift positive reinforcement learning (Packard and White, 1991). Dopamine depletion in the hippocampus impairs spatial navigation (Gasbarri et al., 1996). It is, therefore, important to understand how dopamine affects hippocampal synaptic plasticity. Recent work suggests that one form of synaptic plasticity, long-term potentiation (LTP) at the CA1 Schaffer collateral synapses, is facilitated by D1/D5 dopamine receptors (Frey et al., 1990, 1991, 1993; Huang and Kandel, 1995; Otmakhova and Lisman, 1996).

If dopamine mediates the influence of reward on synaptic modification, the issue of timing becomes critical (Montague et al., 1996). During learning, reward and the resulting dopamine signal may occur *after* an appropriate behavioral response to the stimulus (and stimulus-induced activity). It had been shown, however, that to affect LTP, dopamine must be present at the time of induction (Frey et al., 1993; Otmakhova and Lisman, 1996); application just after induction has no effect. It was therefore of interest to explore whether dopamine can affect other forms of synaptic plasticity.

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One way recently activated synapses might be affected is by depotentiation, the reversal of LTP. Previous studies have indicated that there is a brief period (5–10 min) after the LTP-inducing tetanus when synapses are particularly sensitive to depotentiation (the downregulation of previously potentiated synapses). Low-frequency stimulation (LFS), anoxia, or some drugs applied during this period cause depotentiation (Arai et al., 1990; Larson et al., 1993; Staubli and Chun, 1996). Several lines of previous work led us to suspect that depotentiation might be controlled by cAMP and receptors that elevate cAMP, such as dopamine D1/D5 receptors (Kebabian and Calne, 1979; Kimura et al., 1995). Both theoretical (Lisman, 1989, 1994) and experimental (Mulkey et al., 1994) studies of a related synaptic weakening process, long-term depression (LTD), indicate that LTD can be inhibited by cAMP. Unlike depotentiation, LTD does not require the previous induction of LTP and is not produced in mature animal slices or *in vivo* (Larson et al., 1993; Mulkey et al., 1994; Xu et al., 1997). A key reaction in both LTD and depotentiation is the activation of phosphatases (Mulkey et al., 1994; O'Dell and Kandel, 1994; Staubli and Chun, 1996), and there is a well established pathway by which cAMP, acting via cAMP-dependent protein kinase (PKA), can inhibit the activity of protein phosphatase-1 (PP1). Therefore, dopamine might inhibit depotentiation via a cAMP-dependent process. It is this possibility that we have analyzed in this paper. Our findings provide strong support for such dopaminergic action and suggest some simple models by which dopamine could affect the storage of information that arrives before dopamine.

MATERIALS AND METHODS

All experimental procedures were similar to those previously described (Otmakhova and Lisman, 1996). Transverse hippocampal slices (400 μm thick) were prepared from 17- to 25-d-old Long–Evans rats. During the experiment, slices were perfused on both sides with aerated (95% O_2/5% CO_2) artificial cerebrospinal fluid (ACSF) at 29.2–30.2C°. ACSF contained (in mM): NaCl 120, $NaHCO_4$ 26, NaH_2PO_4 1, KCl 2.5, $CaCl_2$ 2.5, $MgSO_4$ 1.3, and D-glucose 10.

A glass recording electrode filled with ACSF (r = 0.2–0.3 MΩ) was placed in the stratum radiatum of the CA1 region. Two monopolar stimulating electrodes (glass pipettes filled with ACSF, r = 0.25–0.35

MΩ) were positioned on both sides of the recording electrode ~100–150 μm away from it. The strength of the stimuli was 50–60% of the population spike threshold for baseline test stimulation, the tetanus, and LFS. Test stimulation was alternated between two stimulating electrodes throughout the experiment at constant frequency (0.1 Hz). After establishing a stable baseline (15–30 min), we induced LTP by a single tetanus, followed shortly by LFS. The tetanus consisted of 10 bursts of four stimuli (100 Hz), with 30 msec intervals between bursts (0.6 sec in all). At 40–60 min later, the same sequence of tetanus and LFS was repeated on the second pathway. One pathway was used for drug application; the other served as a control. The order of drug and control was alternated between slices. Two different protocols of LFS were used in this study: 3 Hz for 3 min or 2 Hz for 10 min of stimulation. Field EPSPs (fEPSPs) were monitored for at least 40 min after the last tetanus or LFS.

Most drugs were purchased from Research Biochemicals (Natick, MA). H-89 was purchased from Calbiochem (La Jolla, CA); dihydrexidine was a gift from Interneuron Pharmaceuticals (Lexington, MA). Drugs usually were dissolved in the ACSF for stock solutions. H-89 was dissolved in DMSO (10 mM), diluted in regular ACSF to 20 μM, and used to incubate slices for 2–3 hr before an experiment. Isoproterenol solutions were prepared freshly, daily. For application, stocks were dissolved in ACSF and oxygenated in a separate reservoir. Only one drug application was done per slice.

For statistical analysis, responses first were collected and averaged in 5 min blocks: 15 min of baseline and 40 min after the tetanus (or LFS). fEPSP slope (mV/msec) and fiber volley amplitude (mV) were calculated, and data for each experiment were normalized relative to baseline. Having "control" and "drug" pathways in each slice reduced variability and made it possible to see drug effects in individual experiments. After a minimum of four experiments we analyzed the normalized results for each drug, using two-way ANOVA for repeated measurements: df = 1 for the drug factor, df = 7 for the time factor, and df = 7 for the drug·time interaction (Microsoft EXCEL program package). A significant drug effect was present if the F value was >4.043 ($p < 0.05$); the higher the value of F, the larger the effect. If the result was uncertain, we increased the number of experiments to reach a more reliable conclusion. A paired t test was used as a *post hoc* criterion to determine the presence of a drug effect within each 5 min period after the drug application. A high T (low p) value indicated reliability (similarity not only in sign, but also in magnitude) of the effect from slice to slice. To demonstrate this feature in our figures, we plot the average "drug–control" difference at each time period and its significance in a paired t test. For some graphic presentations, data were collected and averaged in 1 min blocks. We used Microcal ORIGIN statistical package for the regression analysis and linear fitting.

RESULTS

To establish a protocol for investigating depotentiation, we first studied the effect of several key variables. Experiments were conducted by standard field recording methods. LTP was induced by a tetanus (see Materials and Methods). The fEPSP measured 40 min after LTP induction was 140 ± 2.5% of the pretetanus baseline (Fig. 1*A*). Strong and reliable depotentiation was induced by 10 min of 2 Hz of LFS given 5 min after the tetanus. The residual LTP 40 min later was only 112 ± 2.1% (Fig. 1*A*). To study a form of depotentiation susceptible to both enhancement and inhibition by neuromodulators, we found that it was desirable to have an induction protocol that by itself produced only partial depotentiation. Therefore, we analyzed the effects of a weaker LFS protocol: 3 Hz/3 min stimulation. The magnitude of depotentiation depended on the delay of LFS after LTP induction (Fig. 1*A*). If the delay was 0.5 min, LTP was reversed almost totally; the residual potentiation 40 min after LFS was 109 ± 3%. If the delay was 5 min, the residual potentiation was 121 ± 1.9%. With longer delays (10 to 30 min), depotentiation was small and unreliable. These results generally confirm previous studies showing that LTP is most vulnerable to depotentiating stimuli within a brief period after LTP induction (Arai et al., 1990; Larson et al., 1993; Staubli and Chun, 1996). We conclude that 3 Hz/3 min LFS

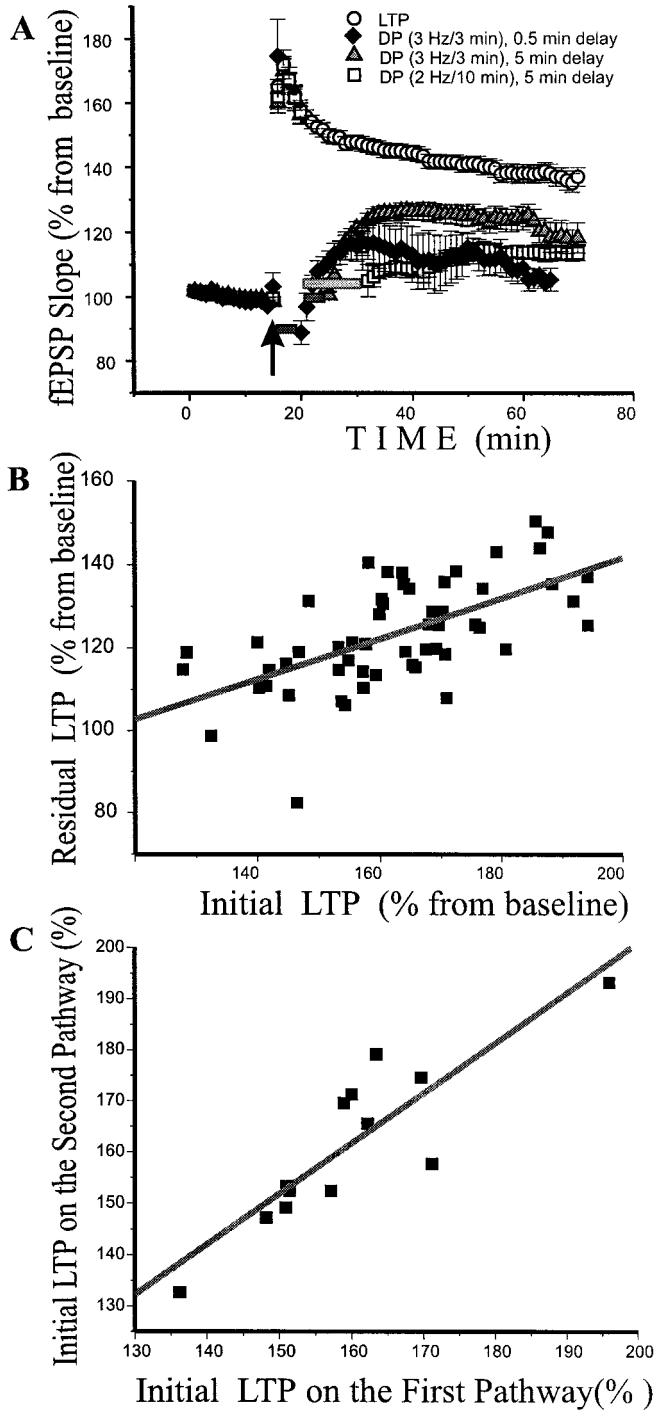

Figure 1. Properties of depotentiation and LTP. *A*, The magnitude of depotentiation depends on the time after the tetanus and the type of low-frequency stimulation (LFS). The average LTP ($n = 39$) induced by a tetanus is shown as a reference. Depotentiation was strong when LFS (3 Hz/3 min) was applied shortly (0.5 min) after the tetanus ($n = 4$). If LFS started 5 min after the tetanus, depotentiation with this LFS was weak ($n = 21$). Stronger depotentiation was produced by 2 Hz/10 min LFS ($n = 15$) than by the 3 Hz/3 min protocol ($n = 21$). The tetanus is marked by an *upward arrow*; *bars* mark LFS. *B*, The residual LTP 40 min after LFS was proportional to initial LTP magnitude (measured 5 min after the tetanus). For the scatter diagram and regression line, $A = 51.4\%$, $B = 0.45$; $n = 55$; correlation coefficient $r = 0.62$; $p < 0.0001$. *C*, Between slice variability of initial LTP values is much higher than within slice variability for different pathways. For the scatter diagram and regression line, $A = 4.8\%$, $B = 0.98$; $n = 13$; correlation coefficient $r = 0.87$; $p < 0.0001$.

starting 5 min after the tetanus is an appropriate protocol for examining how neuromodulators affect depotentiation.

To detect such effects, we found that it was useful to understand some of the sources of variability in LTP and depotentiation. Regression analysis in control experiments (Fig. 1*B*) shows that the residual potentiation after 3 Hz/3 min LFS depends on the magnitude of initial LTP (measured 5 min after the tetanus). The magnitude of LTP varied substantially between slices (SD = 16.9%; $n = 39$); however, its magnitude in two pathways of the same slice was very similar (regression line coefficient $B = 0.98$; Fig. 1*C*). For the detection of drug effects, it was therefore optimal to compare drug and control conditions by using two pathways in the same slice (Otmakhova and Lisman, 1996) with a two-way ANOVA for repeated measurements and a *post hoc* paired *t* test (see Materials and Methods). The ANOVA tables also give an estimate of the time factor contribution and the drug·time interaction. The time factor was usually not significant for depotentiation, and we did not observe significant drug·time interactions. None of the drugs that we used changed the amplitude of the fiber volley, indicating that axon excitability was unaffected.

D1/D5 dopamine receptor activation blocks depotentiation

We first studied the effect of the D1/D5 dopamine receptor agonist (±)6-Chloro-PB (10 μM; Figs. 2*A*, 3*A*). The drug was applied starting 5 min before LTP induction. Then LFS was given 5 min after LTP induction, and the drug was removed. Figure 2*A* shows that this dopamine agonist completely blocked depotentiation (compared with control depotentiation $F = 23.6118$; $p < 0.0001$; $n = 6$). A strong block of depotentiation also was produced by another D1/D5 agonist, dihydrexidine (10 μM; $F = 70.84$; $p < 0.0001$; $n = 4$) (Table 1). Yet another dopamine agonist, (+)-bromo-APB (5 μM; $F = 7.89$; $p < 0.007$; $n = 5$), produced a significant but weaker effect. As we have already noted (Otmakhova and Lisman, 1996), none of the agonists affected baseline synaptic transmission.

As a further test of the involvement of D1/D5 receptors, we checked whether the effect of 6-Chloro-PB could be inhibited by the D1/D5 antagonist (+)SCH 23390 (5 μM). First the antagonist was applied alone for 5 min and then it was coapplied with 10 μM 6-Chloro-PB. Five minutes after the start of coapplication, LTP was induced in one pathway, followed 5 min later by LFS (3 Hz/3 min). The results of this coapplication were compared with the control "tetanus–LFS" stimulation sequence in a second pathway. The antagonist substantially inhibited the effect of D1 agonist 6-Chloro-PB (Fig. 2*B*). The agonist effect was not blocked entirely ($F = 14.01$; $p < 0.001$; $n = 4$), but drug–control differences never reached the 0.05 level of significance in a paired *t* test. Taken together, these results indicate that activation of D1/D5 receptors can inhibit depotentiation substantially.

D1/D5 agonist affects depotentiation and LTP independently

Because D1/D5 agonist can enhance LTP (Otmakhova and Lisman, 1996), it was possible that changes in depotentiation might be secondary to changes in LTP (Fig. 1*B*). To explore this possibility, we performed experiments in which the timing of dopamine agonist (6-Chloro-PB, 10 μM) application was varied. First we tried to determine whether a dopamine-dependent increase in LTP by itself led to a decrease in subsequent depotentiation even if an agonist was not present during LFS. We applied 6-Chloro-PB for 5 min before the tetanus but removed it before starting LFS. Our results show that, under these conditions, D1/D5 agonist was not effective; depotentiation did not differ from the control ($F = 2.16$; $p > 0.15$; $n = 4$; Fig. 3*B*). Another way to address the same question was to test the effect of D1/D5 antagonist on the possible action of endogenous dopamine released by the tetanus. Frey et al. (1990) reported that a tetanus causes the release of endogenous dopamine from the hippocampal slice. This dopamine facilitates both late (Frey et al., 1990, 1991, 1993) and early LTP (Otmakhova and Lisman, 1996). If dopamine released by the tetanus could affect (decrease) subsequent depotentiation, then application of antagonist during tetanus and LFS should increase depotentiation. However, we did not see any effect of D1/D5 antagonist (+)SCH 23390 (5 μM) on depotentiation ($F = 0.043$; $p > 0.83$; $n = 4$).

Next, we applied the D1/D5 agonist *after* the tetanus, a protocol that does not affect LTP (Otmakhova and Lisman, 1996). The agonist (6-Chloro-PB, 10 μM) was present during subsequent LFS and significantly decreased depotentiation ($F = 42.24$; $p < 0.0001$; $n = 4$; Fig. 3*C*). These results prove that D1/D5 agonist affects depotentiation directly, independently from LTP.

We next asked whether the D1/D5 effect on depotentiation depended on the strength of the depotentiating procedure. To answer this question, we applied 6-Chloro-PB (10 μM) during stronger LFS (2 Hz/10 min). With this stronger stimulation 6-Chloro-PB did *not* affect depotentiation ($F = 3.484$; $p > 0.07$; $n = 4$). In additional experiments we started the agonist application before the tetanus. Although LTP in the first 5 min after the tetanus was increased significantly ($p < 0.05$), depotentiation still was not affected ($F = 0.247$; $p > 0.62$; $n = 4$). We conclude that strong depotentiating procedures can overcome the inhibitory effect of D1/D5 receptor activation.

The D1/D5 effect on depotentiation can be blocked by the inhibition of adenylyl cyclase or PKA

If the D1/D5 action is mediated by adenylyl cyclase (AC), the effect of agonist on depotentiation should be blocked by the AC inhibitor SQ 22536 (100 μM) (Haslam et al., 1978; Feinmark et al., 1983; Ferretti et al., 1996). At this dose, inhibitor blocks the effect of norepinephrine on the afterhyperpolarization (AHP) in CA1 pyramidal cells (Madison and Nicoll, 1986a). We note that SQ 22536 slightly (~2–3%) increased fEPSP slope in the baseline. This increase reached a plateau in the first 2–3 min of application. In the control pathway the baseline returned to normal within 3–5 min of washout.

To determine the role of AC in the D1/D5 effect, we applied SQ 22536 for 5 min alone and then added 10 μM 6-Chloro-PB. Five minutes later LTP was induced by a tetanus, followed in 5 min by LFS. Figure 2*C* shows that SQ 22536 completely blocked the action of D1/D5 agonist on depotentiation. In fact, depotentiation was even larger than in controls ($F = 24.79$; $p < 0.0001$; $n = 4$; Fig. 2*C*). These results suggest that D1/D5 agonist inhibits depotentiation via the activation of AC.

The D1/D5 receptor-induced increase in cAMP could affect plasticity by two different mechanisms: by direct activation of cAMP-dependent ion channels (Pedarzani and Storm, 1995) or indirectly by activating PKA. To distinguish between these possibilities, we performed experiments with the specific PKA inhibitor H-89 (Chijiwa et al., 1990). Slices were presoaked initially in 20 μM solution of H-89 in the incubation chamber and then transferred into the recording chamber with regular perfusion medium (Thomas et al., 1996). In one pathway LTP and depo-

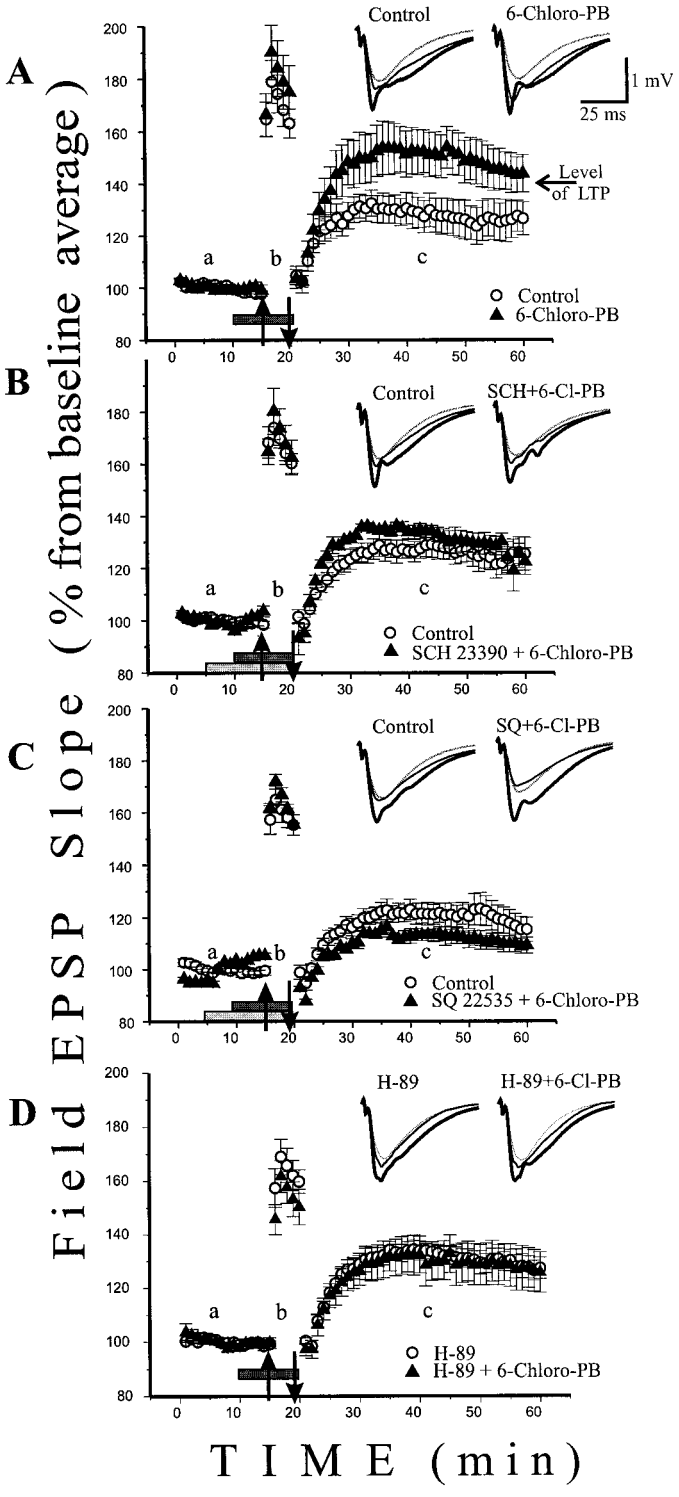

Figure 2. D1/D5 receptor activation inhibits depotentiation acting via adenylyl cyclase. Averaged data and traces of individual experiments (*insets*) were taken in the baseline (*a*, *dotted line*), 2 min after the tetanus (*b*, *thick line*), and 20 min after LFS (*c*, *thin line*). *A*, D1/D5 dopaminergic agonist 6-Chloro-PB (10 μM) inhibits depotentiation. Field EPSP slopes (*solid triangles*) 40 min after LFS in the presence of agonist do not differ from average LTP values (taken from Fig. 1*A* and marked by a *horizontal arrow*). *B*, Agonist action is inhibited by a D1/D5 antagonist (+)SCH 23390, 5 μM. *C*, Agonist action is blocked by the inhibitor of adenylyl cyclase, SQ 22536 (100 μM). *D*, Agonist action is blocked by the pretreatment of the slice with cAMP-dependent protein kinase inhibitor H-89 (20 μM, 2–3 hr). Tetanus is marked by an *upward arrow*, LFS is represented by a *downward arrow*, and agonist application time is shown by a *dark gray rectangle*. SCH 23390 and SQ 22536 perfusions started earlier and are depicted by a *light gray rectangle*. H-89 was introduced by long preincubation but was not present in the perfusion medium.

tentiation were induced in the presence of 6-Chloro-PB (10 μM) and in the other without the agonist. Under these conditions the effect of D1/D1 agonist on depotentiation was no longer observed ($F = 0.55$; $p > 0.45$; $n = 4$) (Fig. 2*D*, Table 1). We conclude that D1/D5 agonist affects depotentiation primarily via a PKA-dependent mechanism.

Effects of AC inhibitor on depotentiation and LTP

To test the role of AC in depotentiation, we applied SQ 22536 (100 μM) alone, starting 10 min before the tetanus and until the end of LFS. SQ 22536 significantly increased depotentiation by ~8% ($F = 7.99$; $p < 0.007$; $n = 4$) (Fig. 4*B*,*F*, Table 1). Variability in the size of the initial and the residual LTP between the slices caused relatively low F value for the drug factor. On the other hand, the effect in each slice was so reliable and reproducible that it caused high T values in a *post hoc* paired t test (Fig. 4*F*). To reduce variability, we performed four additional experiments, using a stronger and more reliable depotentiation protocol (2 Hz/10 min). Under these conditions the increase in depotentiation was stronger and more consistent (14.5%, $F = 40.49$; $p < 0.0001$).

Because application of SQ 22536 started before the tetanus, it was possible that this inhibitor decreased early LTP. If this were the case, the increase in depotentiation might have been secondary to the decrease in LTP. However, additional experiments demonstrated that the application of SQ 22536 (100 μM) for 10 min before the tetanus did not affect early LTP ($F = 0.03$; $p > 0.84$; $n = 6$) (Fig. 4*A*,*E*, Table 1). We conclude that under our experimental conditions AC inhibition promotes depotentiation in the CA1 region without significant effect on early LTP. The absence of any effect of AC inhibitor on LTP was somewhat surprising, because in our previous paper we showed a small decrease in early LTP by D1/D5 antagonist. We proposed that D1/D5 antagonist prevented cAMP elevation by endogenous dopamine released by the tetanus. The reason for this discrepancy is unclear.

Activation of AC mimics D1/D5 effect on depotentiation

If activation of D1/D5 receptor inhibits depotentiation by increasing cAMP, it should be possible to produce a similar effect by the direct activation of AC with forskolin. We have shown previously (Otmakhova and Lisman, 1996) that forskolin application (10 μM), like D1/D5 agonist application, increases early LTP (see also Fig. 4*C*,*E*, Table 1). Figure 4 shows that forskolin completely blocked depotentiation ($F = 35.3336$; $p < 0.0001$; $n = 4$) (Fig. 4*D*,*F*, Table 1). As a result, 30–40 min after the tetanus, fEPSP slopes with and without the LFS did not differ from each other. This suppression of depotentiation by forskolin did not depend on the parameters of LFS. Figure 5 shows that depotentiation induced by a stronger protocol (2 Hz/10 min) also was blocked by 10 μM forskolin with even higher statistical significance ($F = 70.2928$; $p < 0.0001$; $n = 4$). It should be noted that in this case application of forskolin lasted for 20 min. Control experiments have shown that such a long application caused an activity-independent, small (10%) increase in the fEPSP that developed within 5 min after forskolin was removed and persisted for at least

Table 1. Drug effects on LTP and depotentiation in CA3–CA1 synapses

Drug	Effect on LTP, 20–25 min after the tetanus	Effect on depotentiation (3 Hz/3 min) 20–25 min after LFS
6-Chloro-PB, 10 μM	+19.0 ± 2.9**,a	+22.4 ± 6.0**
Dihydrexidine, 10 μM	+22.5 ± 5.4*,a	+18.3 ± 5.3*
(+)-Bromo-APB, 5 μM	+7.5 ± 4.1°,a	+3.2 ± 3.9ns
(+)SCH 23390 (5 μM)	−7.2 ± 3.9°,a	+5.4 ± 4.0ns
6-Chloro-PB, 10 μM, applied before the tetanus, LFS = 3 Hz/3 min		+4.6 ± 4.1ns
6-Chloro-PB, 10 μM, applied after the tetanus, LFS = 3 Hz/3 min		+16.6 ± 5.1*
6-Chloro-PB, 10 μM, LFS = 2 Hz/10 min		−2.6 ± 4.2ns
6-Chloro-PB, 10 μM, applied after the tetanus, LFS = 2 Hz/10 min		−10.5 ± 4.2ns
6-Chloro-PB (10 μM) + (+)SCH 23390 (5 μM)		+7.1 ± 5.1ns
6-Chloro-PB (10 μM) + SQ 22536 (100 μM)		−8.5 ± 5.9ns
6-Chloro-PB (10 μM) + H-89 (pretreatment, 20 μM)		−3.2 ± 5.8ns
SQ 22536, 100 μM	−3.4 ± 6.7ns	−9.2 ± 0.7***
Forskolin, 10 μM	+14.8 ± 7.5°,a	+37.2 ± 4.9**
Forskolin, 10 μM, applied after the tetanus, LFS = 3 Hz/3 min		+9.7 ± 9.3ns
Forskolin, 10 μM, applied after the tetanus, LFS = 2 Hz/10 min		+10.6 ± 2.3**
Isoproterenol, 5 μM	+33.1 ± 14.8°	+13.1 ± 6.5°
Isoproterenol, 5 μM, applied after the tetanus, LFS = 3 Hz/3 min		+9.1 ± 8.9ns
Isoproterenol, 5 μM, applied after the tetanus, LFS = 2 Hz/10 min		+12.0 ± 5.4*
6-Chloro-PB + isoproterenol	+24.7 ± 4.4**	+28.1 ± 6.1**

The data represent "drug − control" differences (mean ± SEM, % from baseline average) for normalized fEPSP slopes in one 5-min (20–25 min) time interval. A plus sign for LTP means it was increased by the drug; a plus sign for depotentiation means it was decreased by the drug. Significance in paired *t* test: ns, $p > 0.1$; °, $p < 0.1$, *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$. *F* and *p* values for the drug factor are listed in the text.

[a]We marked the data taken from previous experiments (Otmakhova and Lisman, 1996) not fully described in this paper.

40 min afterward (Fig. 5). This effect may be related to that produced by long-term application of high (50–100 μM) concentrations of D1/D5 dopamine agonists (Huang and Kandel, 1995). This activity-independent component of forskolin action might contribute in the inhibition of depotentiation with 2 Hz/10 min LFS; however, it obviously is not large enough to account for all of the inhibition produced by forskolin (Fig. 5).

Next we tested whether the effect of forskolin on depotentiation is independent of its action on LTP. We found that forskolin did not affect depotentiation ($F = 2.91$; $p > 0.09$; $n = 4$: Fig. 6*A*) if application started 1 min after the tetanus and continued until the end of LFS (3 Hz/3 min). Such a protocol, however, substantially shortened the application time (from 13 to 7 min), which might explain the negative result. To check this possibility, we started application after the tetanus but used a longer depotentiation protocol (2 Hz/10 min stimulation) so that forskolin application lasted 14 min. With this longer application, forskolin-induced suppression of depotentiation became significant ($F = 14.33$; $p < 0.001$; $n = 4$) (Fig. 6*A*, Table 1), both overall and for each time point. This requirement for a prolonged application might explain our previous failure to see the effect of forskolin on depotentiation (Otmakhova and Lisman, 1995).

Effects of β-adrenoreceptors on synaptic plasticity

The β-adrenoreceptor also is coupled to AC via G_s-protein and has well documented physiological effects on CA1 pyramidal cells (Madison and Nicoll, 1986a,b). This receptor has a substantially higher density than D1/D5 receptors, and it is localized throughout the cell body and dendrites (Swanson et al., 1987). It was of interest to determine whether the activation of β-adrenoreceptors would affect synaptic plasticity in the same way as D1/D5 receptors. The β-receptor agonist, isoproterenol, in doses as low as 10–500 nM affects membrane conductances in pyramidal cells (Dunwiddie et al., 1992; Andrade, 1993), but to assure receptor saturation, we used 5 μM. At this concentration (±)isoproterenol caused a weak (1–3%) and transient (1–2 min) increase in fEPSP at the beginning of application that completely disappeared by the time of the tetanus. Isoproterenol significantly increased early LTP ($F = 44.30$; $p < 0.0001$; $n = 4$; Fig. 6*A*). The magnitude of this increase was very variable between slices so that the paired *t* test significance during individual periods was relatively low: $p < 0.1$. If application started before the tetanus and continued until the end of LFS, isoproterenol also inhibited depotentiation ($F = 22.8741$; $p < 0.0001$; $n = 6$). A similar finding was demonstrated previously in mice (Thomas et al., 1996). In our case, however, the effect of isoproterenol was not so large and reliable as that observed by Thomas and colleagues or that produced by D1/D5 dopamine agonist and forskolin (Fig. 7*B*).

We then examined whether isoproterenol inhibited depotentiation if applied after the tetanus and during LFS (3 Hz/3 min). Unlike the D1/D5 agonist, isoproterenol under these conditions did not affect depotentiation ($F = 1.92$; $p > 0.17$; $n = 4$; Fig. 6*B*). With longer LFS (2 Hz/10 min), however, an isoproterenol effect became significant ($F = 47.22$; $p < 0.0001$; $n = 6$). We conclude that, when β-agonist application is limited to the period of LFS, it can reduce depotentiation, but only with longer applications.

We further explored the relationship between the two agonists, asking whether their effects on plasticity would be synergistic. Coapplication of both agonists for 20 min produced a brief and small increase of baseline at the beginning of application and then again when 20 min of perfusion was stopped. Coapplication significantly increased LTP ($F = 147.49$; $p < 0.0001$; $n = 4$) (Fig. 7*A*, Table 1), but the magnitude of the effect was only a little larger than the D1/D5 dopamine effect alone. When applied until the end of LFS (3 Hz/3 min), the mixture reduced depotentiation

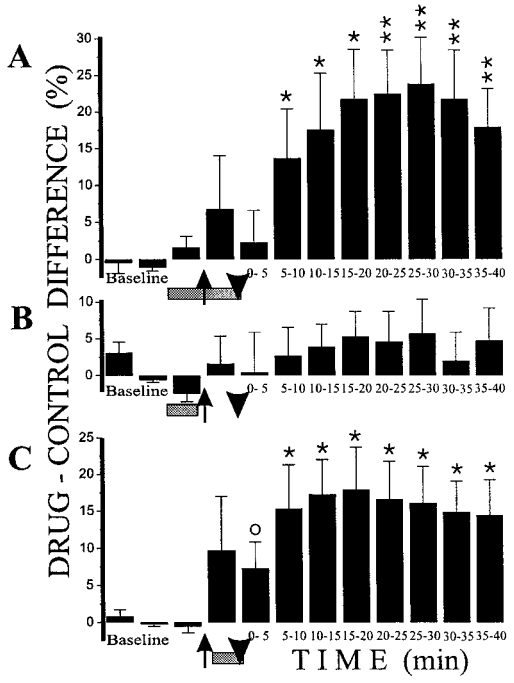

Figure 3. D1/D5 agonist-dependent inhibition of depotentiation depends on the timing of agonist application. Columns represent mean ± SEM for the drug–control differences of the normalized fEPSP slopes in each slice (percentage). The *upward* direction of columns means an inhibition of depotentiation by the drug. *A*, Inhibition of depotentiation was strong when agonist (6-Chloro-PB, 10 μM) was applied starting 5 min before the tetanus and left until the end of LFS (3 Hz/3 min). *B*, When D1/D5 agonist was applied only before and during the induction of LTP, but was absent during LFS, depotentiation was not affected. *C*, Depotentiation was strongly inhibited by D1/D5 agonist applied after the tetanus and during LFS. The time of drug application is marked by the *horizontal bar*; the moment of tetanus is indicated by the *upward arrow*; LFS is shown by a small *downward arrow*. Levels of significance in the *post hoc* paired *t* test: $^{\circ}p < 0.1$; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. *F*, *p*, and *n* values for two-way ANOVA are listed in Results.

($F = 66.46$; $p < 0.001$; $n = 4$) (Fig. 7*B*, Table 1), but not much more strongly than dopamine agonist alone, so there is no simple summation of D1/D5 and β-adrenergic effects on plasticity.

DISCUSSION

D1/D5 receptor activation inhibits depotentiation via cAMP-dependent mechanism

Dopamine has been shown to affect early and late LTP in the hippocampal CA1 pyramidal cells (Frey et al., 1990, 1991, 1993; Otmakhova and Lisman, 1996) and both LTD and LTP in inhibitory striatal neurons (see Calabresi et al., 1997). Our principal result is that activation of D1/D5 receptors of hippocampal CA1 cells greatly reduces the depotentiation produced by LFS (3 Hz/3 min). This effect was quite strong; LFS in the presence of D1/D5 agonist was blocked completely (Fig. 2*A*). The effect was reproducible for three different D1/D5 agonists and was blocked by a D1/D5 antagonist (Fig. 2*B*). This pharmacology is consistent with data showing D1 receptor localization in the stratum radiatum of rat (Huang et al., 1992) and monkey (Bergson et al., 1995). The inhibition of depotentiation was not a secondary consequence of the agonist-induced increase in early LTP (Fig. 3).

The available evidence is consistent with the hypothesis that the effect of D1/D5 receptors on depotentiation is mediated by a cAMP-dependent process. D1/D5 receptors are known to be coupled to AC by the stimulatory G-protein G_s (Kebabian and Calne, 1979; Kimura et al., 1995) and to produce a rise in cAMP (Kebabian and Calne, 1979). We have found that the effect of D1/D5 agonists could be mimicked by forskolin (Fig. 4*D,F*). Furthermore, the effect of D1/D5 activation could be blocked completely by the AC inhibitor SQ 22536 (Fig. 2*C*). If agonist action did not depend on AC activation, there should have been a simple summation of agonist and AC inhibitor effects. Because D1/D5 agonist produced a 20% increase of fEPSP, as compared with control depotentiation, and AC inhibitor decreased fEPSPs by ~8%, the sum result would be an increase. In fact, the "6-Chloro-PB + SQ 22536" mixture actually decreased fEPSP (increased depotentiation) to the same degree as AC inhibitor alone (Fig. 4*B*). This is consistent with D1/D5 receptors acting via a cAMP-dependent second messenger system. Additional evidence for that conclusion was the blockade of agonist effect by the PKA inhibitor H-89 (Fig. 2*D*), suggesting the involvement of cAMP-activated kinase in D1/D5 action.

Our results also provide evidence that AC is involved in the normal process of depotentiation: the AC inhibitor SQ 22536 increased depotentiation (Figs. 4*B,F*, 5), and, as mentioned above, depotentiation was blocked by forskolin (Figs. 4*D,F*, 5). These results are consistent with work on LTD showing that it can be blocked by cAMP analogs (Mulkey et al., 1994). In general, the biochemical similarity of LTD and depotentiation is supported by the demonstration that phosphatase activation is necessary for both LTD (Mulkey et al., 1994; O'Dell and Kandel, 1994) and depotentiation. Because synaptic plasticity can be affected by postsynaptic application of thio-phosphorylated inhibitor 1 (I1) (Mulkey et al., 1994) or Rp-cAMPS (Blitzer et al., 1995), it appears that the biochemistry of synaptic weakening is a postsynaptic process. It is therefore likely that the D1/D5 dopamine effects we have studied are also postsynaptic. In our experiments D1/D5 agonists never affected baseline synaptic responses (Figs. 2, 3, 7). Furthermore the dynamics of fEPSPs in the course of LFS during the induction of depotentiation did not change in the presence of D1/D5 agonists (data not shown) or forskolin (Fig. 5). If the D1 action were presynaptic, one would expect changes in these responses. Finally, D1 receptors have been identified as mostly postsynaptic on hippocampal pyramidal cells (Huang et al., 1992; Bergson et al., 1995).

A specific mechanism by which D1/D5 receptors and cAMP-dependent processes could affect LTD and depotentiation is by influencing a biochemical cascade that controls the strength of synapses (Lisman, 1989, 1994; Mulkey et al., 1994). LTD occurs via the indirect activation of PP1 by the Ca^{2+}-dependent phosphatase 2b, calcineurin. Calcineurin dephosphorylates I1; when dephosphorylated, I1 no longer inhibits PP1. The resulting activation of PP1 leads to a weakening of the synapse, perhaps by dephosphorylation and the resetting of Ca^{2+}–calmodulin-dependent protein kinase II (CaMKII), a protein molecular switch that regulates AMPA channels (McGlade-McCulloh et al., 1993; Tan et al., 1994; Barria et al., 1997). The key action of calcineurin in initiating this cascade can be antagonized by cAMP, because the enzyme that phosphorylates I1 is PKA. Thus, all of the agents that increase cAMP should cause the inhibition of PP1 and thereby inhibit the downregulation of synaptic strength.

The biochemical basis of the fact that depotentiation becomes harder to induce with time after a tetanus remains completely unclear. There actually is a transient period of *activation* of the cAMP-dependent second messenger system 5–15 min after the

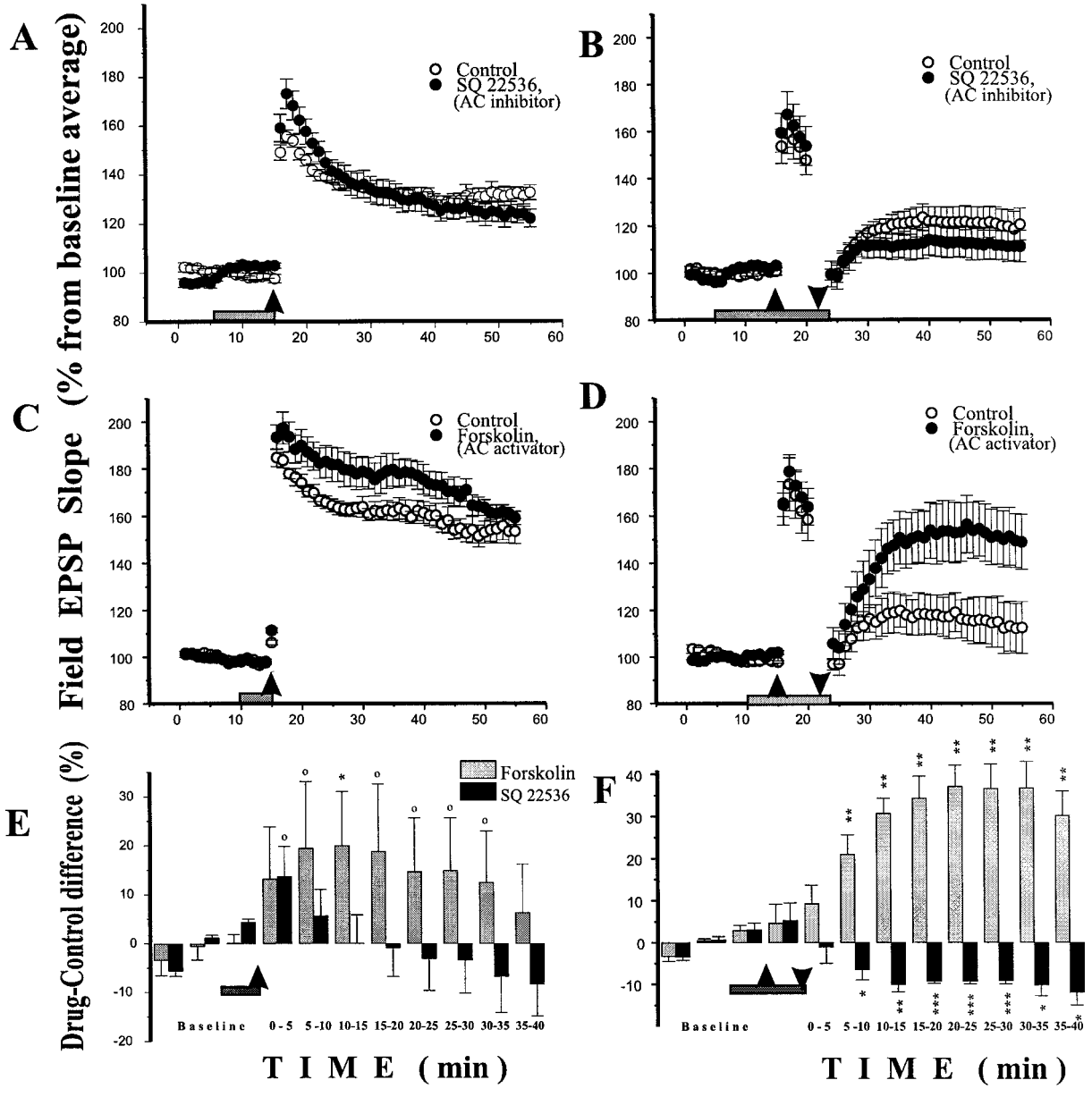

Figure 4. Changes in adenylyl cyclase activity can affect synaptic plasticity. *A*, Adenylyl cyclase inhibitor SQ 22536 (100 μM) did not affect early LTP. *B*, SQ 22536 (100 μM) increased depotentiation. *C*, Adenylyl cyclase activator forskolin (10 μM) increased early LTP. *D*, Forskolin (10 μM) completely blocked depotentiation. Tetanus is marked by an *upward arrow*, LFS (3 Hz/3 min) is represented by a *downward arrow*, and drug application time is shown by a *gray rectangle*. *E*, Forskolin increased early LTP, whereas the adenylyl cyclase inhibitor SQ 22536 did not have any effect. *F*, SQ 22536 increased depotentiation; forskolin completely blocked it. *E* and *F* represent a drug–control difference, by percentage. Calculations and markings are as on Figure 3.

tetanus: the increased level of cAMP (Chetkovich and Sweatt, 1993) and PKA activation (Roberson and Sweatt, 1996) and the reduction of the AHP in the postsynaptic cell (Blitzer et al., 1995). If it were the only time-dependent process induced by the tetanus, it should become progressively easier to induce depotentiation with time, contrary to what is observed. It thus would appear that there is another transient process started by LTP induction that promotes depotentiation. One possibility is that the tetanus leads to a general activation of PP1 by a mechanism that does not involve I1 (Surmeier et al., 1995).

Effects of β-adrenergic receptors on plasticity

Although both D1/D5 and β-adrenoreceptor are coupled to AC, their effects are not identical. Isoproterenol strongly increased early LTP in most slices, but the effect was less reliable than that produced by D1/D5 agonist. We could not inhibit depotentiation by applying isoproterenol during the induction of depotentiation by a weaker LFS (3 Hz/3 min; Fig. 6*B*) under the same conditions in which D1/D5 agonist could inhibit depotentiation (Fig. 3*C*). To affect depotentiation, isoproterenol required longer applications and/or an application beginning before the tetanus. It will be important to determine why D1/D5 dopamine receptors have more powerful effects on depotentiation that β-adrenoreceptors during weak LFS (3 Hz/3 min), whereas strong depotentiation (2 Hz/10 min) is affected more by β-agonist (Fig. 6*B*). Both types of receptors increase cAMP, and the number of β-receptors in the hippocampus is higher (Swanson et al., 1987; Goldsmith and

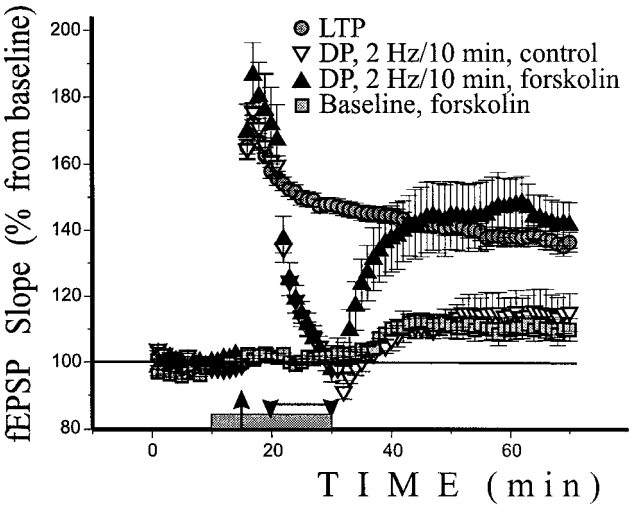

Figure 5. Activity-independent effect of long (20 min) applications of forskolin (10 μM) cannot fully account for forskolin-dependent inhibition of depotentiation. The dynamics of fEPSP during LFS did not depend on the presence of forskolin. Data on LTP ($n = 39$) and on baseline without tetanus or LFS data ($n = 4$) were obtained from different slices. Data with and without forskolin were obtained from the same slices ($n = 4$). The tetanus is marked by an *upward arrow*, LFS (2 Hz/10 min) is represented by the space between the *downward arrows*, and forskolin application is shown by a *gray bar*.

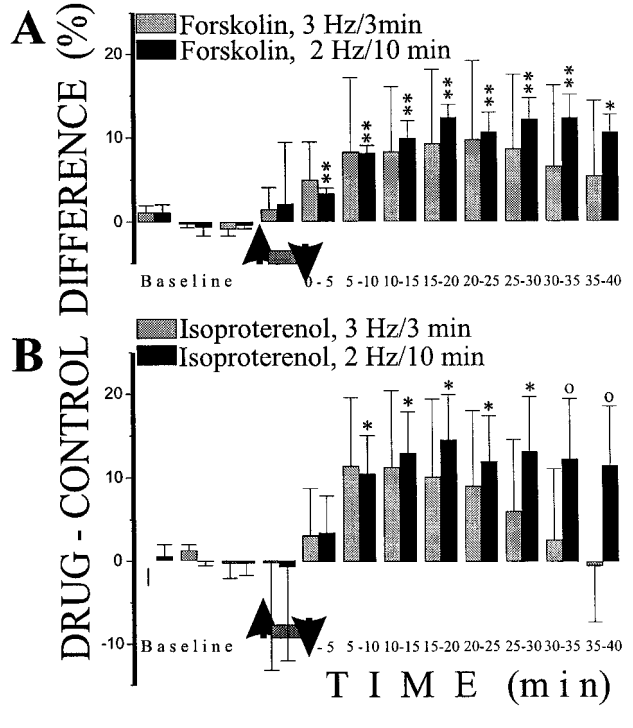

Figure 6. Dependence of forskolin and isoproterenol effects on the timing of application (drug–control difference, by percentage). *A*, When applied after the induction of LTP, forskolin did not affect the depotentiation induced by short LFS (3 Hz/3 min). With increased application time during a longer LFS (2 Hz/10 min), the inhibitory effect of forskolin on depotentiation became significant. *B*, With applications after the tetanus there was no decrease of depotentiation by isoproterenol with short LFS (3 Hz/3 min), but longer applications (2 Hz/10 min) significantly decreased depotentiation. Calculations and markings are as on Figure 3.

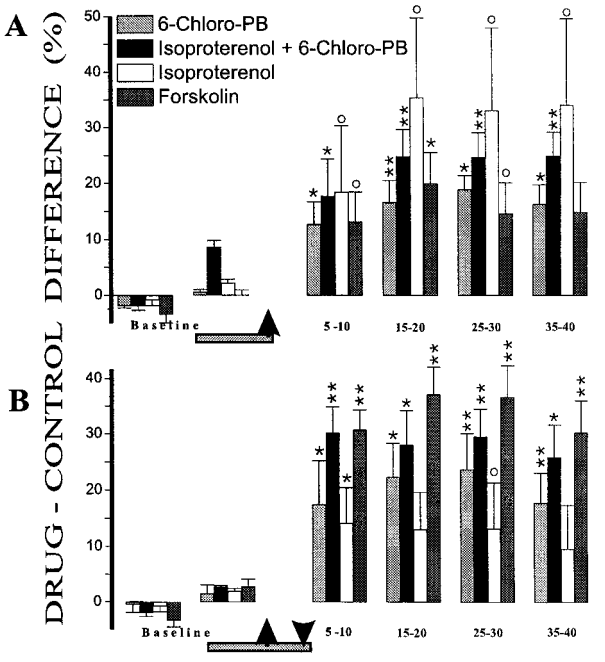

Figure 7. D1/D5 dopaminergic, β-adrenergic agonists, and forskolin effects on synaptic plasticity are not additive (drug–control difference, by percentage). *A*, *Upward bars* show an increase of LTP. Isoproterenol (5 μM) increased LTP the most, but the effect was not reliable. The D1/D5 agonist 6-Chloro-PB (10 μM) strongly and reliably increased early LTP. The effect of coapplication is similar to the D1/D5 agonist effect. The forskolin effect on LTP was the weakest. *B*, *Upward bars* show a decrease of depotentiation; β-agonist isoproterenol (5 μM) applied during both tetanus and LFS produced only weak inhibition of LFS. The dopamine D1/D5 effect was strong and reliable. The largest inhibition of depotentiation was observed either with forskolin application or with coapplication of D1/D5 and β-agonist. Experimental protocols, calculation procedures, and markings are as in Figure 3. To simplify perception, we have not shown all 5 min time intervals in *A* and *B*.

Joyce, 1994). It is possible that the effectiveness of the receptor action is determined by both its density and localization in the cell. D1 receptors were mostly absent from the cell bodies and dendritic shafts but were concentrated on the necks of dendritic spines close to excitatory synapses (Smiley et al., 1994; Bergson et al., 1995). That would allow a precise control over the synapses. On the other hand, β-adrenoreceptors occur in cell bodies and dendritic shafts with high density in CA1 pyramidal cells (Swanson et al., 1987). This suggests that they control the general electrical properties of the cell membrane.

Functional significance of D1/D5 dopamine receptors role in plasticity

The reward-related release of dopamine (Cooper, 1991; Schultz et al., 1993) affects the incorporation of information into long-term memory. Our results indicate that dopamine can affect the processes of activity-dependent synaptic modification, but it remains unclear what type of synaptic modification is affected and when during the learning/consolidation processes dopamine effects actually occur. A key question is how dopamine affects the memory of events that occur before the arrival of dopamine. There are several possibilities. We consider the short tetanic stimulation in our experimental paradigm as a signal to be remembered and D1/D5 dopamine agonist application as reward.

First, dopamine might affect LTP, although dopamine arrived after the tetanus (Fig. 8*A*). According to this view, a signal forms

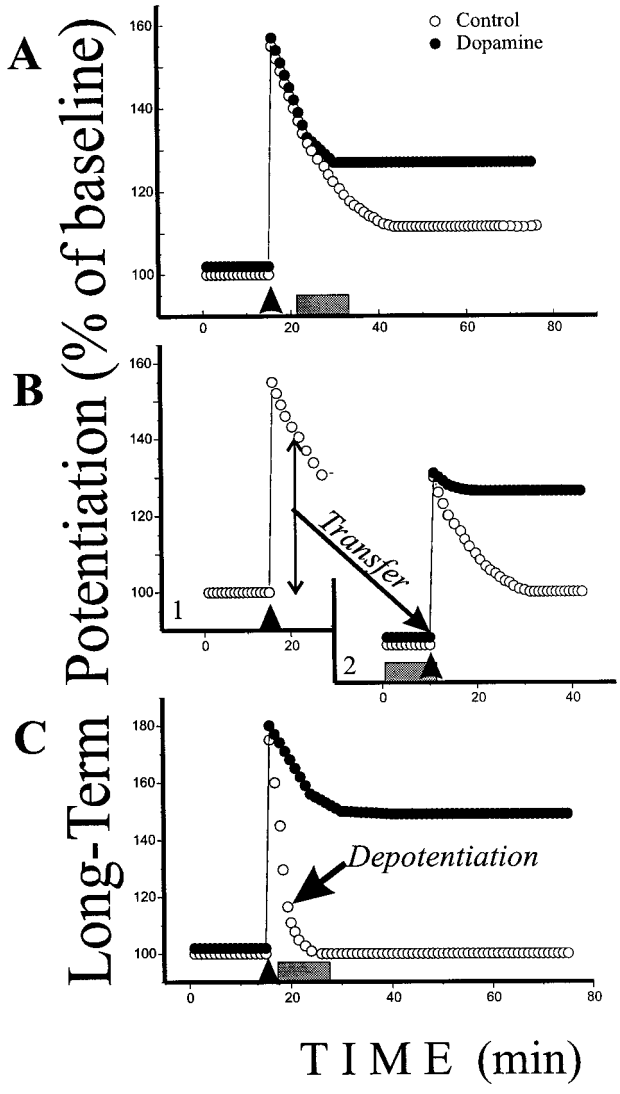

Figure 8. Schematic representation of the role of dopamine in the selection of information for long-term storage. Information input (analog of tetanus) is marked by an *upward arrow*; the reinforcing dopamine signal is shown by a *rectangle*. *A*, Dopamine increases LTP, although it arrives after the tetanus. *B*, Information is maintained initially in a first network and then transferred to the second network, where the activity-dependent storage depends on dopamine. *C*, All information is stored initially for a short time but is subject to erasure (analog of depotentiation, denoted by a *gray arrow*) in the next few minutes. In the presence of dopamine, erasure is blocked.

a lasting biochemical trace on which dopamine can act to enhance or prolong storage. Our previous experiments have not detected such a process: D1/D5 agonist did not affect LTP if applied 15–25 sec after the tetanus (Otmakhova and Lisman, 1996). Even late LTP, the slowly developing phase dependent on CREB phosphorylation and protein synthesis (Frey et al., 1993; Bourtchuladze et al., 1994; Stevens, 1994; Huang et al., 1996), requires the presence of dopamine *during* LTP induction (Frey et al., 1993). Behavioral experiments, however, demonstrate that dopaminergic actions are important even hours after training: intrahippocampal dopamine agonists given at this time improve memory retention and antagonists decrease it (Grecksch and Matthies, 1982; Bernabeu et al., 1997). Based on the properties of LTP in the slice, it seems unlikely that these effects are attributable to an action of dopamine on synapses that underwent LTP several hours before.

A second possibility (Fig. 8*B*) is that dopamine might enhance tetanus-induced LTP if this tetanus were a "replay" of a previous event, a replay that might occur when information was transferred from one network to another (Buzsáki, 1989). The incorporation of information into the second network might involve LTP-like processes and might be enhanced by the presence of dopamine.

The results presented in this paper suggest a third possibility in which *all* information is encoded initially into synapses but then automatically is erased by a depotentiation-like process. This would occur most strongly during the vulnerable period, 5–10 min after incorporation. If, however, dopamine arrived during this erasure, information about the signal would be retained (Fig. 8*C*). The capacity of the brain to store nearly all incoming information is demonstrated in unusual individuals with photographic memory (Luria, 1968). Perhaps it is a defect in the erasure mechanism that allows them to retain unusually large amounts of information.

The view that emerges from this study is that an important action of dopamine in Schaffer collaterals is *to modify the rules of activity-dependent synaptic plasticity*; normal synaptic transmission is not affected. This has important implication not only for learning but also for disease processes, such as schizophrenia and attention deficit disorder, in which dopamine malfunction has been implicated.

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