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D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus

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ABSTRACT **Agonists of the dopamine D1/D5 receptors that are positively coupled to adenylyl cyclase specifically induce a slowly developing long-lasting potentiation of the field excitatory postsynaptic potential in the CA1 region of the hippocampus that lasts for >6 hr. This potentiation is blocked by the specific D1/D5 receptor antagonist SCH 23390 and is occluded by the potentiation induced by cAMP agonists. An agonist of the D2 receptor, which is negatively coupled to adenylyl cyclase through $G_{\alpha i}$, did not induce potentiation. Although this slow D1/D5 agonist-induced potentiation is partially independent of *N*-methyl-D-aspartate receptors, it seems to share some steps with and is occluded by the late phase of long-term potentiation (LTP) produced by three repeated trains of nerve stimuli applied to the Schaffer collateral pathway. Similarly, the D1/D5 antagonist SCH 23390 attenuates the late phase of the LTP induced by repeated trains, and the D1/D5 agonist-induced potentiation is blocked by the protein synthesis inhibitor anisomycin. These results suggest that the D1/D5 receptor may be involved in the late, protein synthesis-dependent component of LTP in the hippocampal CA1 region, either as an ancillary component or as a mediator directly contributing to the late phase.**

Repeated, brief, high-frequency trains of stimuli applied to the Schaffer collateral pathway of the CA1 region of the hippocampus produce a long-lasting synaptic potentiation (LTP; long-term potentiation) that lasts several hours and even days to weeks in the intact animal (1, 2). LTP has recently been dissected into two components, an early transient component (E-LTP) that requires the influx of calcium into the postsynaptic cell through *N*-methyl-D-aspartate (NMDA) receptor channels and the subsequent activation of several serine-threonine and tyrosine kinases (2, 3), and a later more persistent component (L-LTP) that requires new protein and RNA synthesis (4–8). The late component of LTP is mediated, at least in part, by cAMP and by the cAMP-dependent protein kinase, protein kinase A (PKA) (6–9).

How does this late cAMP- and protein synthesis-dependent phase arise? The early phase of LTP is mediated homosynaptically and requires activity only in this monosynaptic Schaffer collateral pathway. Does the late phase depend only on activity in this pathway? Or does the late phase also require a heterosynaptic modulatory component that recruits additional receptors?

One modulatory system known to innervate the CA1 region of the hippocampus is the mesolimbic dopaminergic pathway that ends on both the D1 and D5 dopaminergic receptors coupled to adenylyl cyclase (10, 11). Immunohistochemical localization of D1 and D5 receptors reveals a heavy staining along pyramidal cells and the stratum radiatum (12). Retrograde fluorescent tracers show that dopaminergic fibers that project from the ventral tegmental area innervate the CA1 field (13, 14). At the moment, the D1 and D5 receptors (also designated D1a and D1b) cannot be distinguished pharmacologically. Both are linked to adenylyl cyclase and have a similar pharmacological profile (15). We therefore refer to them collectively as the D1/D5 receptors.

One clue that D1/D5 receptors might be involved in LTP has come from the finding that the late stage of LTP can be blocked by the D1/D5 antagonist SCH 23390 (16). To explore further the possible role of D1/D5 receptor activation in L-LTP, we have addressed five questions: (*i*) Can a specific D1/D5 agonist, when given alone, simulate the late phase of LTP in the CA1 region? (*ii*) If so, is this potentiation mediated by NMDA receptors or by D1/D5 receptors? (*iii*) Does D1/D5 receptor potentiation occlude LTP induced by tetanization of Schaffer collaterals? (*iv*) Is this potentiation mediated by an increase in cAMP (consistent with the coupling of D1/D5 receptors to adenylyl cyclase)? (*v*) Finally, does this potentiation depend on protein synthesis, consistent with its being critical for the late phase? Our experiments suggest that the late phase of LTP is mediated heterosynaptically, at least in part, by a dopaminergic modulatory action mediated through D1/D5 receptors.

MATERIALS AND METHODS

Transversely cut hippocampal slices (400 μm) were prepared from 5- to 6-week-old Sprague–Dawley rats and maintained in an interface chamber with continuous superfusion at 1.5–2 ml/min. The solution composition was 124 mM NaCl, 1.3 mM $MgCl_2$, 4 mM KCl, 1.2 mM KH_2PO_4, 2.0–2.5 mM $CaCl_2$, 25.6 mM $NaHCO_3$, and 10 mM D-glucose, bubbled with 95% O_2/5% CO_2. The temperature of the bath was maintained at 28–29°C. After equilibration of the slices in the chamber for 2 hr, extracellular recordings were performed as described in a previous paper (7). Baseline responses were recorded for 30–60 min before drug application or LTP-inducing tetanization. Four biphasic constant current pulses (0.2 Hz; duration, 0.1-ms pulse) were used to generate test excitatory postsynaptic potentials (EPSPs) at 10-min intervals during the first hour after drug application or LTP induction and at 30-min intervals during the following hours. In LTP experiments an additional test was performed 1 min after tetanization to induce LTP. Three stimulus trains at 100 Hz, 1 s of 0.2-ms pulse duration were used, a tetanization protocol that produces long-lasting potentiation for up to 8 hr (6). The average waveform from four successive responses was saved and the EPSP slope (mV/ms) was measured.

The following drugs were made and stored as concentrated stock solutions and dissolved in the superfusing medium to achieve the final concentrations used: D1/D5 agonist, SKF

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Abbreviations: LTP, long-term potentiation; E-LTP and L-LTP, early and late components of LTP; NMDA, *N*-methyl-D-aspartate; PKA, protein kinase A; EPSP, excitatory postsynaptic potential; APV, (±)-2-amino-5-phosphonopentanoic acid; PPHT, (±)-2-(*N*-phenylethyl-*N*-propyl)amino-5-hydroxytetralin hydrochloride; Sp-cAMPS, adenosine 3′,5′-cyclic monophosphorothioate.

R(+) 38393 HCl (50–100 mM) (Research Biochemicals International, Natich, MA); D1/D5 agonist, 6-bromo-ApB hydrobromide (50–100 mM) (Research Biochemicals International) in dimethyl sulfoxide (DMSO; 0.1% of the final solution); D2 agonist (±)PPHT hydrochloride [(±)-2-(*N*-phenylethyl-*N*-propyl)amino-5-hydroxytetralin hydrochloride] (100 mM) (in DMSO); D1 antagonist, R(+) SCH 23390 (1 mM) (Research Biochemicals International); adenosine 3′,5′-cyclic monophosphorothioate (Sp-cAMPS) Na salt (100 mM) (BioLog Life Sciences Institute, Bremen, Germany); anisomycin (20 mM) (Sigma); (±)-2-amino-5-phosphonopentanoic acid (APV) (50 mM) (Research Biochemicals International).

RESULTS

A D1/D5 Receptor Agonist Simulates the Late Phase of LTP. Dopamine induces a long-lasting synaptic potentiation in hippocampal slices (6, 17). Consistent with these earlier findings, we found that application to the bath of 250 μM dopamine together with 1 mM ascorbic acid produced long-lasting synaptic potentiation (data not shown). To determine whether this potentiation specifically involves the activation of D1/D5 receptors, we used the specific D1/D5 agonist SKF 38393 (50–100 μM) (18) and applied it for 15 min. The D1/D5 agonist produced a persistent increase of the EPSP slope in 11 of 14 slices. As expected of the agonist of a transmitter that selectively induces the late phase of LTP, synaptic potentiation induced by the D1/D5 agonist SKF 38393 had a very slow onset. The potentiation started 50–60 min after application of the agonist and reached a peak 3–4 hr after drug application. The mean potentiation 6 hr after application of SKF 38393 was 163% ± 10% (n = 14; Fig. 1A_1). This action of SKF 38390 was specific for D1/D5 receptors. A specific antagonist of the D1/D5 receptors SCH 23390 prevented the potentiation (Fig. 1A_1).

To further examine the D1/D5 agonist-induced potentiation, we also used another D1/D5 agonist, 6-bromo-ApB. A brief application of 6-bromo-ApB (100 μM) perfused for 15 min (or 50 μM for 30 min) induced a similarly enduring but slightly faster-developing potentiation (156% ± 20% at 3 hr; mean ± SEM; n = 5; Fig. 1B). By contrast, brief application of the D2 receptor agonist PPHT (100 μM), which is negatively coupled to adenylyl cyclase (19), induced only a transient depression lasting 1–2 hr and no significant change 3 hr after washing (Fig. 1C).

To determine whether the D1/D5-induced potentiation was mediated by NMDA receptors, we applied the NMDA antagonist (±)-APV (50 μM) together with the agonist 6-bromo-ApB and continued to perfuse APV into the bath for the next 2 hrs. In the presence of APV, the potentiation induced by 6-bromo-ApB at 2 and 3 hr was reduced substantially to 116% ± 12% and 128% ± 3% (mean ± SEM; n = 5), respectively. This compares to 148% ± 17% and 156% ± 20% in the absence of APV at the same time points ($P < 0.05$; Student's t test). Thus, the D1/D5 agonist-induced potentiation is in part dependent on NMDA receptor activation and in part seems independent of the NMDA receptor. This is consistent with our earlier findings (6), that the increase in cAMP produced by the three trains necessary to induce L-LTP can be blocked in one of two ways: by NMDA receptor blockers or by antagonists of the D1/D5 receptors.

Analogs of cAMP Occlude the Action of a D1 Agonist. The long-lasting synaptic potentiation can be induced by Sp-cAMPS, an activator of the cAMP-dependent PKA (6). Because the D1/D5 receptor is linked to adenylyl cyclase, we next examined whether cAMP occludes the potentiation induced by D1/D5 agonists. We pretreated slices for 15 min with Sp-

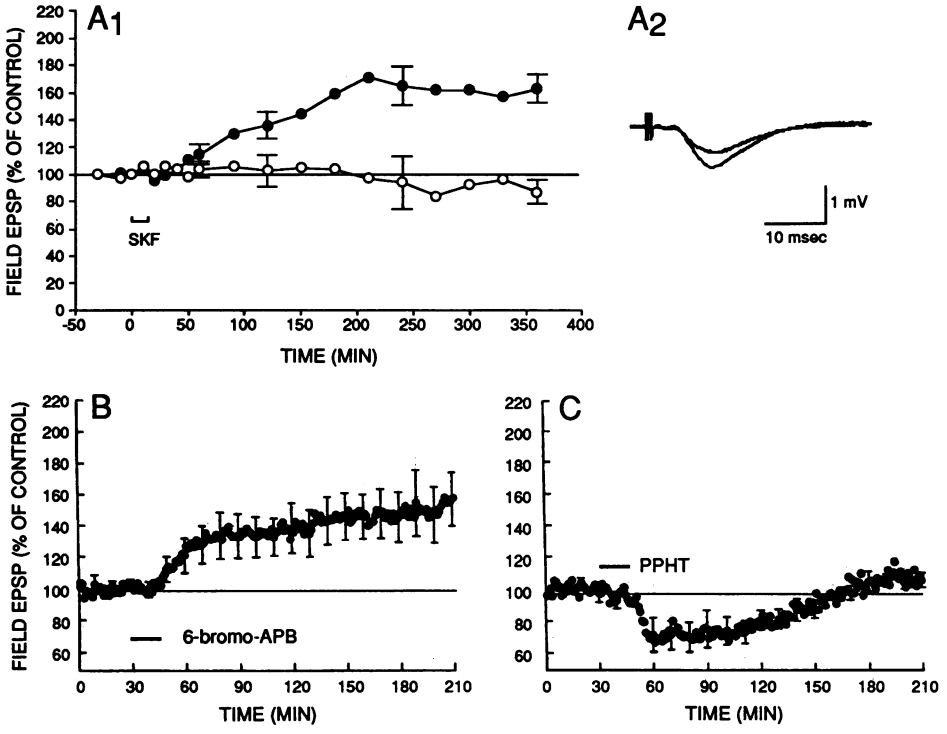

FIG. 1. (A) A D1 agonist induced long-lasting synaptic potentiation. (A_1) SKF 38393 (●) (50 μM; 15 min) applied into bath medium (bar) induced an increase in the slope of EPSP, lasting longer than 6 hr (mean ± SEM; n = 14). Combined application of D1 antagonist SCH 23390 (2 μM; 30 min) with SKF 38393 (○) prevented the SKF-induced potentiation (n = 5). (A_2) Representative averages of four consecutive field EPSPs obtained before and 6 hr after the application of SKF 38393. (B) The D1 agonist 6-bromo-ApB (100 μM), applied to the bath medium for 15 min, induced a similar long-lasting synaptic potentiation (mean ± SEM; n = 5). A constant low-frequency stimulus (0.016 Hz) was used in the experiments described in B and C. Slopes of EPSP for each stimulus were plotted and averaged. (C) The D2 agonist PPHT (100 μM) applied for 15 min induced a transient depression and no significant change of synaptic potential 3 hr after washing (mean ± SEM; n = 4).

cAMPS (100 μM) in the bath. Consistent with previous results (6), application of Sp-cAMPS induced a long-lasting synaptic potentiation. Two hours after drug application, when the potentiation reached a stable level (164% ± 18%; $n = 6$), the intensity of the stimulus was reduced to bring the EPSP back to its initial baseline level. Fifteen minutes later the D1/D5 agonist SKF 38393 was applied. The D1/D5 agonist produced no further synaptic potentiation in the pathway already potentiated by the PKA agonist (Fig. 2). This occlusion by cAMP of the potentiation produced by the D1/D5 agonist suggests that the D1/D5-induced potentiation shares one or more steps with the cAMP pathway.

A D1/D5 Agonist Occludes L-LTP. To examine the relationship between D1/D5-induced potentiation and L-LTP induced by tetanic stimulation of the Schaffer collateral pathway, we performed two sets of occlusion experiments. First, we produced L-LTP by tetanization of the Schaffer collaterals and then applied the D1/D5 agonist to the slice. In the pathway already potentiated by tetanization, application of the D1/D5 agonist induced no extra increase of the EPSP slope (Fig. 3*A*). Second, we reversed the procedure and applied the D1/D5 agonists prior to tetanization to see whether it would selectively occlude L-LTP. Three hours after D1/D5-induced potentiation, stimulation intensity was reduced to the baseline level and three trains were applied to induce LTP. Since D1/D5 receptor activation appears to contribute only to the late phase of LTP, one would predict no occlusion of the early phase. Indeed, a substantial amount of E-LTP could be induced at the start, but the induced LTP began to decay ≈90 min after tetanization and reached 126% ± 10% ($n = 7$) by 180 min (Fig. 3*B1*). Thus, compared to LTP in control slices, there was no clear decrease of E-LTP at 30 and 90 min (Fig. 3*B2*). By contrast, there was a significant decrease of L-LTP as evident at 3 hr after tetanization [126% ± 10% ($n = 7$), as compared to 156% ± 8% ($n = 11$) in control slices; $P < 0.05$, Student's t test; Fig. 3*B2*].

A D1/D5 Antagonist Blocks the Late Phase of LTP. These occlusion experiments suggest that D1/D5-induced potentiation shares at least some of the same steps with the late phase of tetanus-induced LTP. To further confirm the involvement of the D1/D5 receptor in the late phase of LTP, we examined the effect of the D1/D5 receptor antagonist SCH 23390 by using two tetanization protocols that have been shown to induce E-LTP and L-LTP (7). Respectively, in the absence of tetanization, SCH 23390 (0.1 μM) caused no significant

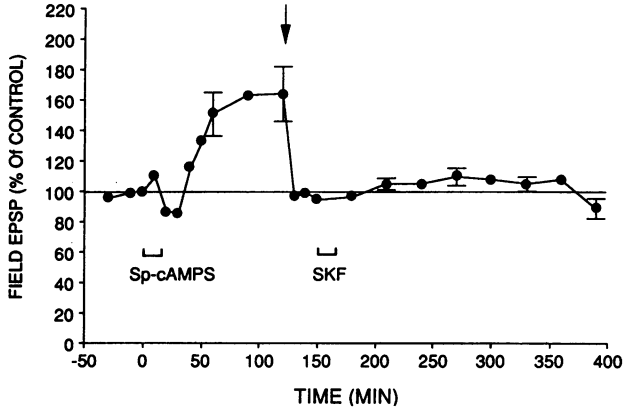

FIG. 2. Relationship between synaptic potentiation induced by a PKA agonist and a D1/D5 receptor agonist. Bath application of the PKA agonist Sp-cAMPS (100 μM; 15 min) induced a long-lasting potentiation. The stimulus intensity was then reduced to generate EPSPs of the control slope 2 hr after Sp-cAMPS application (arrow), and a D1/D5 agonist, SKF 38393, was applied (50 μM; 15 min). The application of SKF 38393 failed to induce long-lasting potentiation after Sp-cAMPS-induced potentiation ($n = 6$).

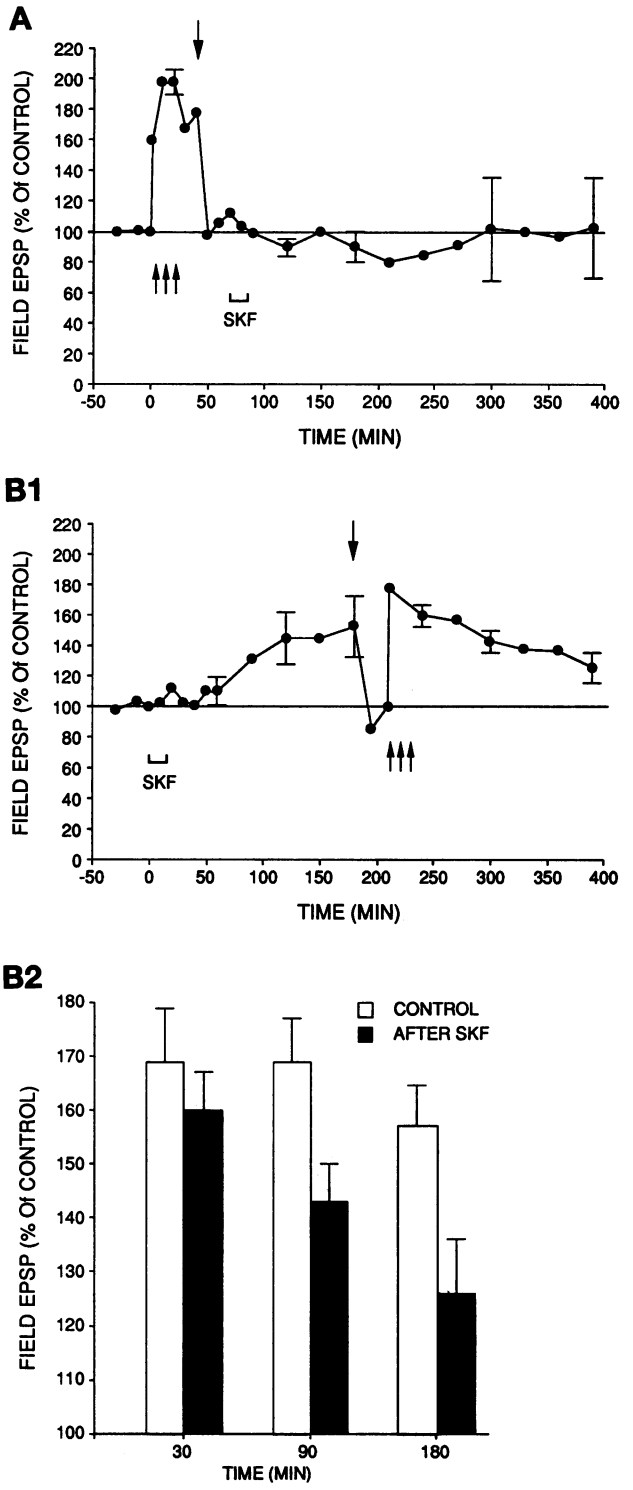

FIG. 3. Relationship between the D1/D5-induced potentiation and tetanic LTP. (*A*) Effect of a D1 agonist after tetanic LTP. Triple tetanization (arrows) induced a large amount of potentiation. The intensity of the stimulus was then reduced to generate EPSPs of the control slope (top arrow) and SKF 38393 was applied (50 μM; 15 min). Note that SKF 38393 failed to induce long-lasting potentiation after tetanic potentiation ($n = 6$). (*B1*) LTP after D1/D5-induced potentiation. The application of SKF 38393 induced a long-lasting potentiation. The intensity of stimulus was reduced to generate EPSPs of the control slope 3 hr after drug application (top arrow) and three tetani (bottom arrows) were given. (*B2*) Comparison of the amount of LTP in a control slice ($n = 11$) and in slices prepotentiated by D1/D5 agonist ($n = 7$) induced by triple tetanization (100 Hz; 1 s; 0.2-ms pulse duration). Note that the LTP was significantly decreased 3 hr (but not 30 min and 1.5 hr) after tetanization in D1/D5 agonist-treated slices.

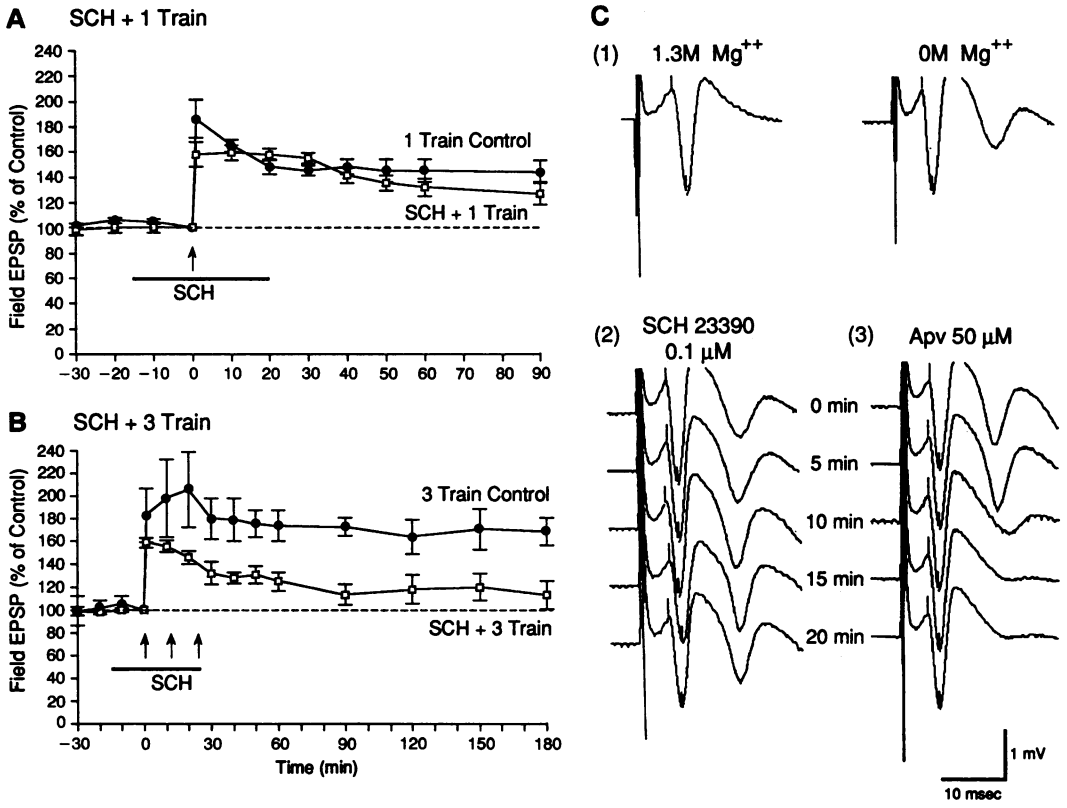

FIG. 4. Blockade of LTP by D1/D5 antagonist. (*A*) SCH 23390 (0.1 μM) had no effect on LTP induced by one tetanus (100 Hz; 1 s; 0.2-ms pulse duration). (*B*) SCH 23390 (0.1 μM) depressed LTP induced by triple tetanization (arrows). (*C*) The D1/D5 antagonist had no effect on the NMDA-mediated component of the field potentials. (*C1*) An NMDA-mediated component of the population spike was elicited when the Mg^{2+} was washed from the perfusion solution. (*C2*) Application of the D1/D5 antagonist SCH 23390 (0.1 μM) has no effect on this component (n = 5). (*C3*) The NMDA antagonist (±)-APV (50 μM) completely abolishes this component 15 min after drug application (n = 5).

changes in the baseline synaptic response. By contrast, SCH 23390 depressed the expression of the later phase of LTP induced by three trains of tetanization (100 Hz; 1 s; 0.2-ms pulse duration). A significant decrease of the EPSP slope was seen 3 hr after the last of three trains used to induce LTP [117% ± 8% (n = 12), as compared with 169% ± 10% (n = 9) in the drug-free solution; $P < 0.01$; see Fig. 4*B*]. This result is similar to the earlier report by Frey *et al.* (16). By contrast, SCH 23390 had no effect on LTP induced by a single train of tetanization (Fig. 4*A*). As a control, we also examined the effects of the D1/D5 antagonist on the NMDA receptor-mediated component of the population spike in Mg^{2+}-free solution (20) and found that SCH 23390 had no effect on this component, suggesting that the D1/D5 antagonist does not produce its effect on LTP through an action on the NMDA receptor (Fig. 4*C*).

The Potentiation Induced by the D1/D5 Agonist Is Blocked by Inhibitors of Protein Synthesis. The late phase of LTP produced by three trains requires protein synthesis (5, 21). We have therefore examined the effects of anisomycin (20 μM), a protein synthesis inhibitor, on the D1/D5 receptor agonist-induced potentiation. In the presence of anisomycin, SKF 38393 did not stimulate any long-lasting synaptic potentiation (Fig. 5). Six hours after application of the D1/D5 agonist in the presence of anisomycin the potentiation was 90% ± 10% (n = 6), which is significantly different from the potentiation with the D1/D5 agonist alone (163% ± 10%; n = 14; $P < 0.01$). Anisomycin alone had no effect on baseline synaptic response (Fig. 5). These results suggest that potentiation induced by D1/D5 receptor agonists requires new protein synthesis.

DISCUSSION

We provide here further evidence that the late phase of LTP may be mediated, at least in part, heterosynaptically by a dopaminergic modulatory input acting on a D1/D5 receptor. A specific D1/D5 receptor agonist can simulate the late phase of LTP. This action requires new protein synthesis and is selectively blocked by specific antagonists of the D1/D5 receptors. The action of dopamine seems to be mediated via cAMP, and it occludes both the cAMP-induced potentiation and the tetanus-induced late phase of LTP. Since both the D1 and the D5 receptors stimulate adenylyl cyclase (19), it is not possible to distinguish between them on pharmacological grounds. Therefore, the results obtained by using the D1/D5 receptor agonists or antagonists in this study could be mediated by either the D1 receptor, the D5 receptor, or both.

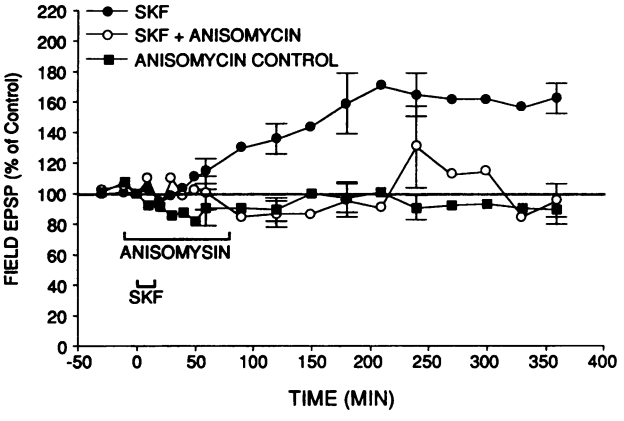

FIG. 5. Protein synthesis dependence of D1/D5 agonist-induced potentiation. The protein synthesis inhibitor anisomycin blocked D1 agonist-induced potentiation. Anisomycin was applied to the bath solution (20 μM; 90 min). The application of SKF 38393 failed to induce long-lasting potentiation in the presence of anisomycin (n = 6), while anisomycin alone had no effect on baseline EPSPs (n = 5).

Particularly interesting is the finding that the potentiation induced by D1/D5 receptor agonists is slow in its onset, starting 50–90 min after drug application and reaching a peak after 3–4 hr. This time course resembles the late phase of LTP induced by tetanization and by cAMP (6, 7, 21) and is much slower than other pharmacological manipulations that induce synaptic potentiation, including NMDA, glutamate, and tetraethylammonium (22–24).

The D1/D5-mediated potentiation seems to result from functional coupling with adenylyl cyclase and cAMP, a coupling that may represent the common step shared by both the D1/D5-mediated potentiation and the late phase of LTP induced after stimulation of the Schaffer collaterals. This conclusion is consistent with the finding that the potentiation produced by D1/D5 agonist is occluded by pretreatment with a PKA activator or by tetanus-induced L-LTP and with earlier findings by Frey *et al.* (6) that L-LTP occludes the Sp-cAMPS-induced potentiation of field EPSP. Conversely, the fact that occlusion of L-LTP by the D1/D5 receptor agonist is delayed is also consistent with the finding that cAMP occludes LTP only 90 min after tetanization (6, 7). The involvement of the D1/D5 receptor in LTP through its functional coupling to cyclase is also supported by the finding that the D1/D5 antagonist and the PKA inhibitor have a similar effect on LTP (7). However, our evidence for dopamine participation does not exclude other signaling pathways that might also contribute to the late phase of LTP.

Given the finding that the late phase of LTP seems heterosynaptically mediated, how is the dopaminergic input activated? Does repeated electrical stimulation which activates the Schaffer collaterals also recruit activity in the dopaminergic fibers that course through the CA1 region? Or does glutamate, released from the terminals of the Schaffer collaterals during activity, act on glutamate receptors in the dopaminergic terminals so as to release dopamine without requiring impulse activity in the dopaminergic fibers themselves? Our experiments do not distinguish between these two possibilities. But one clue comes from the finding that the late phase of LTP induced by tetanization is partially dependent on the NMDA receptor (25). The increased release of dopamine after tetanization (26) might be mediated at least in part by activation of the NMDA receptors on the presynaptic terminal of the dopaminergic fibers. Alternatively, activation of postsynaptic NMDA receptors could induce the release of a retrograde messenger such as nitric oxide, which could stimulate the transmitter release from the dopaminergic terminals (27). In fact, increased concentrations of dopamine and norepinephrine have been observed in hippocampal and striatal slices after exposure to NO (28, 29).

Behavioral studies suggest that the dopaminergic system, and particularly the D1/D5 receptors coupled to adenylyl cyclase, may be important for certain forms of learning and memory. For example, local injection of the D1/D5 receptor antagonist SCH 23390 into prefrontal cortex induced errors and increased latency in performance on a memory-guided task (30), and injection of the D1/D5 receptor agonist interferes with hippocampal-based tasks (31). Assuming that synaptic potentiation is positively correlated with spatial learning, our finding that the D1/D5 receptor is involved in the expression of hippocampal LTP provides initial insights into how a modulatory transmitter in the mammalian brain might affect long-term memory storage by selectively affecting only the late phase of LTP.

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