

A DOUBLE DISSOCIATION WITHIN THE HIPPOCAMPUS OF DOPAMINE D₁/D₅ RECEPTOR AND β-ADRENERGIC RECEPTOR CONTRIBUTIONS TO THE PERSISTENCE OF LONG-TERM POTENTIATION

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Abstract—We compared the effects of the D₁/D₅ receptor antagonist SCH-23390 with the β-adrenergic receptor antagonist propranolol on the persistence of long-term potentiation in the CA1 and dentate gyrus subregions of the hippocampus. In slices, SCH-23390 but not propranolol reduced the persistence of long-term potentiation in area CA1 without affecting its induction. The drugs exerted reverse effects in the dentate gyrus, although in this case the induction of long-term potentiation was also affected by propranolol. The lack of effect of SCH-23390 on the induction and maintenance of long-term potentiation in the dentate gyrus was confirmed in awake animals. The drug also had little or no effect on the expression of inducible transcription factors. In area CA1 of awake animals, SCH-23390 blocked persistence of long-term potentiation beyond 3 h, confirming the results in slices. To rule out a differential release of catecholamines induced by our stimulation protocols between brain areas, we compared the effects of the D₁/D₅ agonist SKF-38393 with the β-adrenergic agonist isoproterenol on the persistence of a weakly induced, decremental long-term potentiation in CA1 slices. SKF-38393 but not isoproterenol promoted greater persistence of long-term potentiation over a 2-h period. In contrast, isoproterenol but not SKF-38392 facilitated the induction of long-term potentiation.

These data demonstrate that there is a double dissociation of the catecholamine modulation of long-term potentiation between CA1 and the dentate gyrus, suggesting that long-term potentiation in these brain areas may be differentially consolidated according to the animal's behavioural state. © 1999 IBRO. Published by Elsevier Science Ltd.

Key words: hippocampus, dentate gyrus, LTP, dopamine, noradrenaline, inducible transcription factor.

Long-term potentiation (LTP) of excitatory synaptic connections of the hippocampus typically requires glutamate release and activation of *N*-methyl-d-aspartate (NMDA) receptors for its induction.⁸ While glutamate receptor activation is necessary for induction of LTP, it may not be sufficient to achieve maximal levels of induction, or to establish the late forms of LTP. To elicit optimal LTP, co-activation of extrinsic inputs such as catecholamine-releasing afferents appears to be necessary. Thus, for example, dopamine (DA) D₁/D₅ receptor antagonists have been shown to slightly decrease the induction of LTP in area CA1,³² but more dramatically, they

prevent LTP from persisting more than a few hours,^{17,18} despite the use of strong tetanization protocols that should produce ample activation of NMDA receptors. Correspondingly, administration of D₁/D₅ agonists can induce a slow-onset potentiation of responses that has similar characteristics to the late, protein synthesis-dependent, phase of LTP.²³ This appears to involve the triggering of a biochemical cascade that includes activation of adenylate cyclase, activation of protein kinase A and subsequent *de novo* protein synthesis. Another prominent hippocampal catecholamine, noradrenaline (NA), does not appear to play such a vital role in LTP in CA1. Although administration of the β-adrenergic agonist isoproterenol lowers the LTP threshold,³⁷ β-adrenergic antagonists do not block LTP induction.¹⁵ To date, the effects of these drugs on the persistence of LTP in CA1 have not been investigated.

DA-containing fibres from the midbrain A9 and A10 cell groups innervate both area CA1 and the dentate gyrus regions of the hippocampus.³⁸ In

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Abbreviations: ACSF, artificial cerebrospinal fluid; DA, dopamine; EPSP, excitatory postsynaptic potential; ITF, inducible transcription factor; LTP, long-term potentiation; NA, noradrenaline; NMDA, *N*-methyl-d-aspartate.

contrast to CA1, the extent to which DA modulates LTP in the dentate gyrus is poorly understood, although one recent report has shown that a D₁/D₅ receptor antagonist can block the induction of a mildly induced LTP in this brain region. On the other hand, numerous reports have indicated that NA potently modulates LTP in the dentate gyrus, since β -adrenergic receptor antagonists severely reduce the induction of LTP, while administration of β -adrenergic agonists alone can induce LTP in medial perforant path synapses.^{14,41}

The pattern of monoaminergic modulation of LTP reviewed above suggests that CA1 and the dentate gyrus may be differentially regulated by DA and NA, respectively, particularly with regard to the persistence of LTP. This differentiation may have importance for the consolidation of LTP in different behavioural states, since DA and NA are thought to be preferentially released under different behavioural conditions.^{3,4,27} Accordingly, we set out to directly compare the catecholamine regulation of LTP persistence across hippocampal subregions. Some of this work has been reported previously in preliminary fashion.⁴⁴

EXPERIMENTAL PROCEDURES

In vitro experiments

Hippocampal slices (400 μ m) were prepared from young adult male Sprague–Dawley rats (200–300 g; University of Otago Animal Breeding Station) using methods described previously,²⁵ except that the animals were initially anaesthetized with ketamine (100 mg/kg). All efforts were made to minimize animal suffering, to reduce the number of animals used and to utilize *in vitro* preparations where possible. All experiments were conducted in accord with the University of Otago's Code of Ethical Conduct for the Manipulation of Animals, and relevant New Zealand legislation. Dissection and slicing of the hippocampus (400 μ m thickness) were performed using ice-cold artificial cerebrospinal fluid (ACSF), except for the dentate gyrus experiments, in which the ACSF was kept at room temperature during these procedures. Area CA3 was routinely removed from all slices by a manual knife-cut. Slices were transferred to a recording chamber and superfused at 2 ml/min with ACSF (32.5°C; saturated with 95% O₂/5% CO₂; in mM): 124 NaCl, 3.25 KCl, 1.25 NaH₂PO₄, 26 NaHCO₃, 2.5 CaCl₂, 1.3 MgCl₂ and 10 d-glucose. For experiments in the dentate gyrus, the GABAergic antagonist picrotoxin (1 μ M; Sigma) was added to the bathing solution to facilitate LTP induction.

Following a 2-h recovery period, extracellular excitatory postsynaptic potentials (EPSPs) were evoked and recorded in either the stratum radiatum of area CA1 or the middle molecular layer of the dentate gyrus, using a monopolar tungsten stimulating electrode (75 μ m diameter) and a glass recording microelectrode, filled with 2 M NaCl (1–3 M Ω). Positioning of stimulating and recording electrodes in the medial perforant path of the dentate gyrus was confirmed by the presence of paired-pulse depression, induced by two stimuli given 50 ms apart. Slices showing a >2 mV EPSP amplitude were accepted for the experiment. The stimulation current strength (0.1 ms pulse width) was adjusted to produce a 1-mV field EPSP during baseline recordings. During the 45-min baseline recording period, sets of four test pulses (5-s intervals) were given every 5 min. To induce LTP, three trains of conditioning

stimulation were delivered at 10-min intervals, each train of pulses being given at 100 Hz (twice pulse duration) for 1 s. Following tetanization, four test pulses (5-s intervals) were given 1, 11, 21, 30, 60, 90, 120, 150 and 180 min after the first train. Because the focus of these experiments was on the persistence of LTP, slices were excluded from analysis if tetanization elicited <20% initial LTP, or if the responses fell below –20% of the baseline values at any time. The initial slopes of the field EPSPs were measured off-line, and the responses to the four pulses were averaged at each time-point. Student's *t*-tests were performed to assess group differences, using a *P* < 0.05 confidence level.

A 1 mM stock of SCH-23390 (D₁/D₅ receptor antagonist; Research Biochemicals) was made in a saline solution, then diluted to a final concentration of 1 μ M in ACSF. Care was taken to use the drug in a darkened room. A 1 mM stock of propranolol (β -adrenergic antagonist; Sigma) was made in a saline solution, then diluted in ACSF to a final concentration of either 1 or 0.1 μ M. Isoproterenol (Sigma) and SKF-38393 (Research Biochemicals) stocks were made in saline solution and diluted 1000-fold to reach final concentrations of 0.5 and 150 μ M, respectively. In order to allow for a possible facilitation of LTP persistence by the receptor agonists, a tetanus protocol weaker than that used above was employed, namely five bursts of pulses, five pulses per burst at 100 Hz, with 200 ms between bursts. This protocol induced a moderate and decaying form of LTP in control slices. In these experiments, no LTP induction criterion was applied. For all experiments, the agonists and antagonists were bath-applied 10–20 min prior to, and through, the tetanization period.

In vivo experiments

Adult male Sprague–Dawley rats (300–450 g) were anaesthetized with sodium pentobarbital (Nembutal; 60 mg/kg, i.p.). For the dentate gyrus experiments, stimulating and recording wire electrodes were implanted in the angular bundle (to activate a mixed population of medial and lateral perforant path fibres) and in the hilus of the dentate gyrus, respectively, as described previously.¹ The electrodes were placed to maximize the positive-going field EPSP and population spike. For the CA1 experiments conducted in separate animals, stimulating and recording wire electrodes were implanted into the stratum radiatum of area CA1 using the following coordinates (from bregma, in mm): recording electrode, 3.6 posterior, 2.3 lateral; stimulating electrode, 3.8 posterior, 2.3 lateral. The electrodes were placed to maximize the negative-going field EPSP recorded in the stratum radiatum.

The animals were allowed two weeks to recover from surgery, after which the quality of the field potentials was assessed.¹ Stimulation during baseline recordings consisted of 60–135 pulses (0.05 Hz, 100–150 μ s) at stimulus strengths that evoked either a 3- to 4-mV population spike (with a minimum EPSP slope of 3.5 mV/ms; dentate gyrus) or an EPSP 25% of maximum (maximum EPSP amplitude had to be at least 6 mV; CA1). These were continued across days until the responses stabilized. One tetanization protocol used for the perforant path afferents to the dentate gyrus consisted of 10 bursts of five tetanic trains (400 Hz, 250- μ s pulses), as described previously.¹ Such stimulation produces a protein synthesis-dependent late phase of LTP (LTP₃) that decays with an average time constant of about three weeks.¹ A second tetanization protocol used for both area CA1 and the dentate gyrus consisted of three 500-ms trains (100-Hz pulses, at baseline pulse strength), separated by a 10-min interval. Post-tetanic responses at the baseline stimulation strength were monitored for 60–180 min post-tetanus, and for up to two weeks post-tetanus in some groups of animals. EPSP initial slopes

were monitored for both hippocampal subregions, while dentate gyrus population spike amplitudes were also monitored. D_1/D_5 receptors were blocked using SCH-23390 (5 mg/kg/ml, i.p.) made up in a saline vehicle. This dose is well above that found previously to antagonize D_1/D_5 receptor activation *in vivo*.⁴⁷ Recordings for each animal were made in a single recording chamber, at approximately the same time of day, for the duration of the experiment.

The methods used for immunohistochemistry were identical to those described in detail by Abraham *et al.*¹ Briefly, rats were deeply anaesthetized with ether 1 h after tetanization of the perforant path fibres, and perfused transcardially with saline followed by 4% paraformaldehyde. Seventy-micrometre-thick coronal sections of the dorsal hippocampus were cut on a Vibratome and sections were immunostained using antibodies to c-Jun, JunB, Fra, Krox 24 and Krox 20. The amount of immunostaining was quantified using the MD30 image analysis system (Leading Edge) and a video camera mounted on a Leitz diaphan microscope. This involved taking average density measurements over the entire dentate granule cell layer at $\times 40$ magnification on both the tetanized and control hemispheres. The tetanized hemisphere values were normalized as a percentage of the control hemisphere values in the same animal.

RESULTS

Dissociation of D_1/D_5 receptor contribution to long-term potentiation between CA1 and the dentate gyrus in vitro

Since numerous previous studies have shown that D_1/D_5 receptor antagonism blocks LTP persistence in area CA1, we attempted to replicate this finding using SCH-23390, and then repeated these experiments in the dentate gyrus for comparison purposes. Tetanization (three trains at 100 Hz, twice pulse duration) in control slices led to a robust LTP in CA1 that was relatively stable over a 3-h period (EPSP 3 h post-tetanus: $40 \pm 8\%$, $n = 6$). Slices treated with SCH-23390 (1 μ M) showed normal LTP induction, but then a nearly complete decay of this LTP over the ensuing 3-h period ($6 \pm 8\%$, $n = 6$, $P < 0.02$ relative to drug-free controls; Fig. 1A). The decay of LTP in the drug-treated slices was not simply due to a direct effect of the SCH-23390 on the evoked responses, as drug-treated slices not given tetanization showed responses that remained near baseline levels both during drug treatment and throughout the subsequent recording period (EPSP at the end of recording: $-3 \pm 9\%$, $n = 6$; Fig. 1A).

To test whether SCH-23390 exerts a similar effect on LTP persistence in the dentate gyrus, a similar stimulation and drug treatment experimental protocol was run in the dentate gyrus for medial perforant path synapses. Once again, tetanization led to a robust and stable LTP in the drug-free slices ($46 \pm 10\%$, $n = 7$; Fig. 1B). In contrast to CA1, however, SCH-23390 had no effect on either the induction or the maintenance of LTP in the dentate gyrus ($44 \pm 9\%$, $n = 5$).

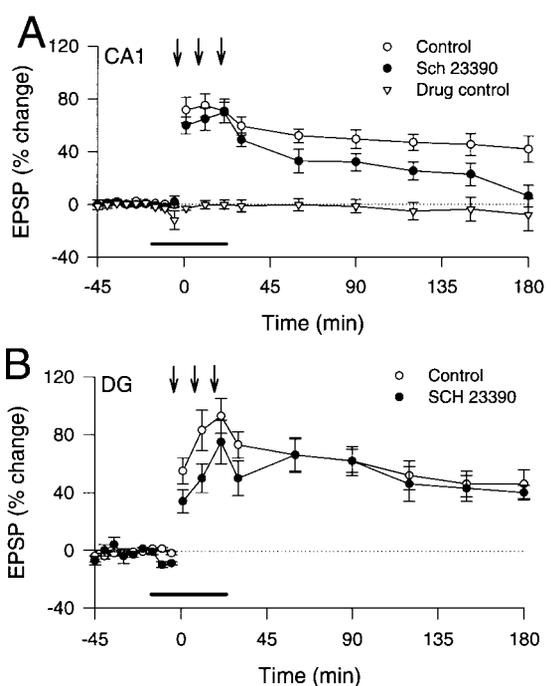


Fig. 1. D_1/D_5 receptor activation is necessary for maintenance of LTP in area CA1 but not the dentate gyrus *in vitro*. (A) Field EPSPs evoked by periodic episodes of four pulses (0.2 Hz) delivered to the Schaffer collaterals were recorded in the stratum radiatum of area CA1. LTP was induced by three 100-Hz trains spaced 10 min apart, as indicated by the arrows. Bath application of the D_1/D_5 receptor antagonist SCH-23390 (1 μ M) significantly reduced persistence of LTP over a 3-h period. Slices exposed to SCH-23390 but not given tetanization showed no significant change in the EPSP slope (drug control). (B) The effect of SCH-23390 on LTP was also assessed for the medial perforant path projections to the dentate gyrus (DG), using virtually identical procedures to those described above for CA1. SCH-23390 had no effect on the induction or maintenance of LTP in the dentate gyrus. Solid lines indicate the time of drug application. Data in this and all ensuing figures represent mean \pm S.E.M. percentage change in the EPSP slope relative to pre-tetanus (pre-drug) values.

Dissociation of β -adrenergic receptor contribution to long-term potentiation between CA1 and the dentate gyrus in vitro

To test whether LTP in CA1 is modulated by another catecholamine, NA, we repeated the above experiments using the β -adrenergic receptor blocker propranolol. In contrast to the effects of SCH-23390 in this region, neither LTP induction nor its persistence were significantly affected by propranolol (1 μ M) administration during the tetanus (EPSP 3 h post-tetanus: $32 \pm 11\%$, $n = 6$, $P > 0.5$ relative to untreated control slices; Fig. 2A). When tested in the dentate gyrus, however, the same concentration of propranolol severely attenuated the induction of LTP, and caused the residual LTP to decay rapidly over the subsequent 3-h recording period ($13 \pm 11\%$, $n = 5$, $P < 0.05$ relative to untreated control slices; Fig. 2B). These were not simply effects of the drug on synaptic transmission, as

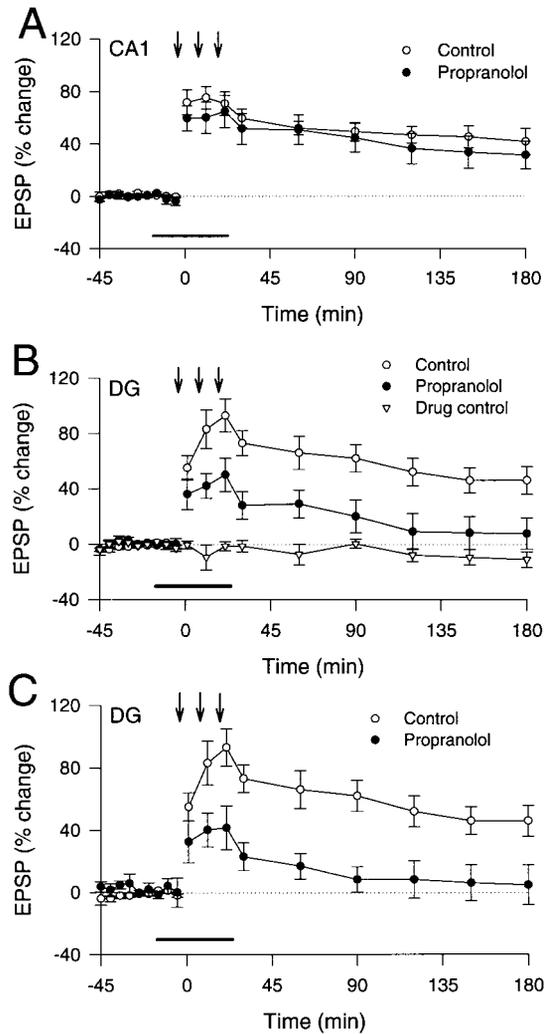


Fig. 2. β -Adrenergic receptor activation is necessary for LTP maintenance in the dentate gyrus but not in area CA1 *in vitro*. (A) Bath application of the β -adrenergic antagonist propranolol (1 μ M) had no significant effect on the maintenance of LTP in area CA1 over a 3-h period. (B) In the dentate gyrus, both the induction and the maintenance of LTP were dramatically reduced in the presence of propranolol as compared to control slices. Bath application of propranolol without the tetanus did not affect baseline synaptic transmission (drug control). (C) A 10-fold lower dose of propranolol also reduced LTP induction and maintenance in the dentate gyrus. Solid lines indicate the time of drug application. Arrows indicate time of 100-Hz tetanic stimulation.

drug-treated slices ($n=7$) not given tetanization showed responses that remained near baseline levels during both the drug treatment and the subsequent recording period (drug control; Fig. 2B). A 10-fold lower dose of propranolol (0.1 μ M) exerted similar effects on LTP induction and persistence (LTP at 3 h: $5 \pm 13\%$, $P < 0.05$ relative to control slices; Fig. 2C).

Overall, the data from the first two experiments clearly demonstrate a double dissociation between the LTP modulating effects of SCH-23390 and propranolol across the CA1 and dentate gyrus

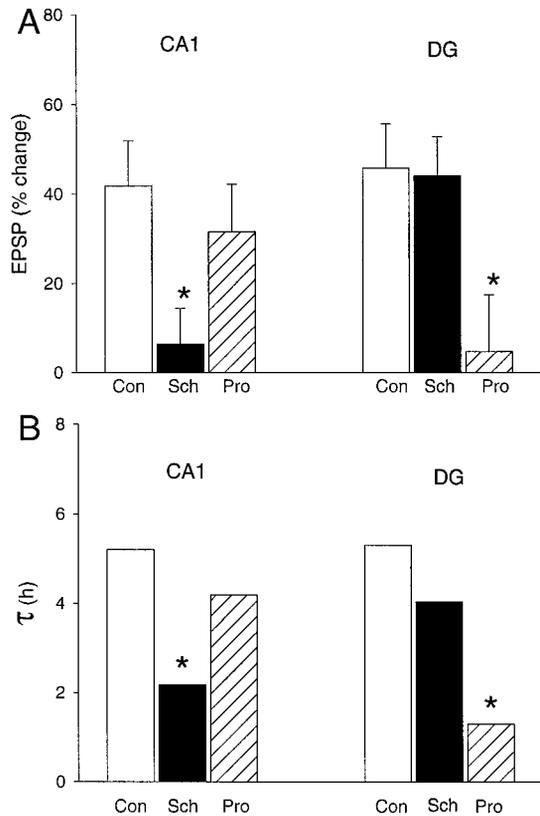


Fig. 3. Summary histograms of the persistence of LTP, showing the double dissociation of effects between drugs and hippocampal subregions. (A) In area CA1, SCH-23390 (Sch) but not propranolol (Pro) blocked the maintenance of LTP, compared to control (Con) slices. In contrast, propranolol but not SCH-23390 blocked the maintenance of LTP in the dentate gyrus. Data indicate the mean \pm S.E.M. degree of LTP measured 3 h after the first train of stimulation. (B) A similar double dissociation was found in the rate constant of LTP decay, taken from the second exponential of a double exponential fit. For clarity, data are represented as the time constant of decay (τ) in hours, which is calculated as the inverse of the rate constant value. It is inappropriate to take the inverse of the measures of variability, however, and thus these are not illustrated. * $P < 0.05$ relative to control, Student's *t*-test (A) or Mann-Whitney *U*-test (B).

subregions of the hippocampus. D_1/D_5 receptor blockade potentially blocked persistence of LTP in CA1 but not the dentate gyrus, while the converse pattern of results was true for β -adrenergic blockade (Fig. 3A). To confirm the differential drug effects on LTP persistence, double exponential functions were fit to the post-tetanus data for each slice. The mean rate constant of decay for the second (slower) exponential was calculated and averaged for each group. The data confirm the more rapid decay of LTP in both the SCH-23390-treated CA1 slices and the propranolol-treated dentate gyrus slices (Mann-Whitney *U*-test: $P < 0.05$; Fig. 3B). Overall, these results strongly support the view that endogenous catecholamine release is vital for the stabilization of LTP, but interestingly, areas within the hippocampus are differentially responsive to DA versus NA signalling.

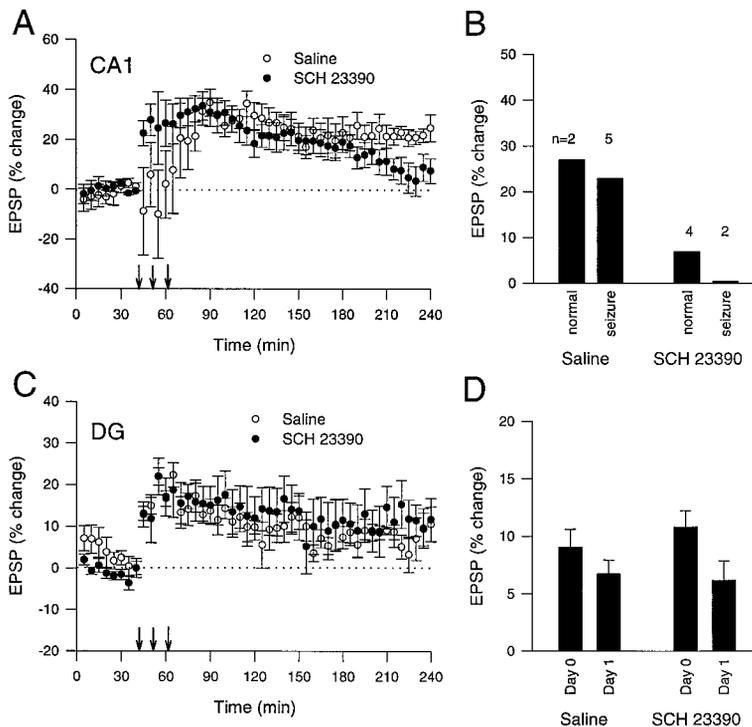


Fig. 4. Regional difference in the effect of SCH-23390 on the late phase of LTP *in vivo*. (A) In area CA1, injection of SCH-23390 (5 mg/kg) 2 h prior to high-frequency stimulation (100 Hz, 500 ms, arrows) did not affect the initial induction of LTP, but caused a faster decay over the 3-h post-tetanus recording period. The low values for the saline-treated group early after the tetani were due to response suppressions associated with mild epileptiform afterdischarges. (B) The frequency of occurrence of electrographic afterdischarges was somewhat higher in the saline-treated group, but this did not account for the differential degree of LTP decay between drug groups. Data represent the mean percentage change in EPSP slope measured 3 h post-tetanus for animals that either did (seizure) or did not (normal) show afterdischarges. The number of animals per subgroup is given above each bar. (C) In the dentate gyrus, SCH-23390 did not affect induction or persistence of LTP when employing the same tetanus protocol as used for CA1. (D) Mean percentage change \pm S.E.M. in the field EPSP slope 3 h (day 0) and 24 h (day 1) after tetanic stimulation. Note that the LTP is much less robust in the dentate gyrus after this tetanus protocol than in area CA1.

Dissociation of D₁/D₅ receptor contribution to long-term potentiation between CA1 and the dentate gyrus in vivo

Because most afferents are severed when slices are prepared, modulation of LTP by spontaneously active catecholamine afferents would not be readily detected using this preparation. Accordingly, we have repeated the SCH-23390 experiments in awake animals, to determine whether there is a DA modulation of LTP in the dentate gyrus that is detectable in the intact brain.

To confirm that D₁/D₅ receptor activation affects LTP in CA1 *in vivo*, and to provide a positive drug control for the dentate gyrus experiments, we initially tested whether SCH-23390 affects induction or persistence of LTP in area CA1. SCH-23390 (5 mg/kg, i.p.), administered 2 h prior to tetanization, had no effect on the initial induction of LTP in area CA1. Thirty minutes after the last tetanus, robust LTP of the EPSP was seen in both saline-treated control ($33 \pm 5\%$, $n = 7$) and drug-treated groups ($32 \pm 6\%$, $n = 6$; Fig. 4A). By 3 h post-tetanus, however, the LTP in the SCH-23390-treated group had decayed

back to near baseline values ($5 \pm 4\%$), which was significantly different from the LTP that still remained in the saline-injected group ($23 \pm 3\%$, $P < 0.01$).

Tetanization in CA1 *in vivo* is prone to producing epileptiform afterdischarges, and occasionally behavioural convulsions. Any animals showing behavioural convulsions were discarded from the above experiment. A number of them, however, exhibited afterdischarges without obvious behavioural signs, and these were included in the study. Since seizures have been reported to prolong or stabilize LTP in the dentate gyrus,⁵ we analysed whether there were any group differences in the occurrence of afterdischarges that may have accounted for the differential LTP decay in CA1. While five of seven saline-treated animals showed afterdischarges, only two of six SCH-23390-treated animals did so. This difference was not significant by a chi-square test. Furthermore, when we grouped the data according to whether afterdischarges were observed or not, it was apparent that the degree of LTP remaining 3 h after tetanus was much more related to the treatment group rather than to the presence of afterdischarges

(Fig. 4B). Thus, we conclude that the lack of LTP persistence in the SCH-23390-treated group was due to D₁/D₅ receptor blockade, rather than an absence of afterdischarges.

Having confirmed that the effect of SCH-23390 on CA1 LTP maintenance *in vivo* mirrored that seen *in vitro*, we tested the drug's effect on LTP in the dentate gyrus, using the same drug and tetanization protocols. Four animals were given either saline or SCH-23390 (5 mg/kg) 2 h prior to receiving three 100-Hz trains. After LTP had decayed to baseline, the treatments were crossed over for the same four animals. Neither the induction nor the maintenance of LTP over 3 h was affected by SCH-23390. LTP of the field EPSP 3 h post-tetanus was $9 \pm 2\%$ in the saline condition and $11 \pm 1\%$ in the drug condition (Fig. 4C). Furthermore, LTP on the day following tetanization was also not different between groups (saline: $7 \pm 1\%$; SCH-23390: $6 \pm 2\%$; Fig. 4D). Similarly, no differences between groups in population spike LTP were observed (data not shown).

Because the LTP induced by three 100-Hz tetani was not robust nor very long lasting in the dentate gyrus, additional experiments were conducted using a 50-train (400 Hz) protocol, which produces a large LTP decaying with a time constant of about three weeks.¹ In the first of these experiments, SCH-23390 or saline vehicle was administered 30 min prior to perforant path tetanization. There was no effect of the SCH-23390 on basal perforant path synaptic transmission, and robust LTP was induced in both control and drug groups. In addition, no significant differences were seen in the amount of LTP of the EPSP between the control ($32 \pm 5\%$, $n = 6$) and drug groups ($33 \pm 4\%$, $n = 7$, $P > 0.05$; Fig. 5A) at 1 h post-tetanus. LTP of the population spike at 1 h post-tetanus was also not significantly different between the control ($455 \pm 144\%$, $n = 6$) and drug groups ($604 \pm 180\%$, $n = 7$, $P > 0.05$; Fig. 5B).

Since SCH-23390 has been reported to affect the late phase of LTP more than the initial induction, we also followed the persistence of perforant path LTP across the first 14 days post-tetanus ($n = 4$ per group). A two-way analysis of variance with repeated measures across time revealed a significant gradual decrement of LTP over the 14-day period for both the EPSP data ($F_{6,36} = 4.32$, $P < 0.01$) and the spike data ($F_{6,36} = 5.80$, $P < 0.001$; Fig. 5C, D). However, there was no significant effect of drug treatment for either measure. For the EPSP measure, but not the spike, there was a significant drug by time interaction ($F_{6,36} = 3.57$, $P < 0.01$), but post hoc Dunnett's *t*-tests failed to detect a significant difference between the two groups at any individual time-point.

Because a 2-h drug injection–tetanization interval proved effective in blocking LTP maintenance in CA1 (Fig. 4), we ran a second experiment using this protocol in the dentate gyrus for a separate

group of animals (SCH-23390: $n = 7$; control: $n = 6$). Once again, there were no significant drug effects on either basal synaptic transmission, initial LTP induction or the persistence of LTP across 14 days (data not shown). In this experiment, there was no drug by time interaction for persistence of EPSP LTP across the 14 days post-tetanus.

SCH-23390 has been reported to affect the constitutive expression of inducible transcription factors (ITFs) in the striatum,²⁹ and so may have affected ITF expression in the dentate gyrus after LTP induction in the present experiments. If so, this would present an important dissociation of ITF expression from LTP persistence. We found, however, that the expressions of various zinc-finger-containing (Zif/268 and Krox 20) and leucine-zipper-containing (Fos-related, c-Jun, JunB) ITF proteins 1 h after LTP induction were relatively unaltered by SCH-23390 ($n = 4$) compared to saline-injected controls ($n = 5$). These groups of animals did not differ in the degree of LTP induced, measured 20 min post-tetanus. While there was a tendency for the ITF response to be slightly weaker for all proteins tested, only c-Jun (which was only marginally expressed in control tissue anyway) showed a statistically significant reduction in the SCH-23390-treated group (Student's *t*-test, $P < 0.05$; Fig. 6). The overall weak effect of SCH-23390 on ITF protein expression corresponded well with its general lack of effect on induction and persistence of LTP in the dentate gyrus.

In summary, the *in vivo* experiments confirmed the finding in slices that activation of D₁/D₅ receptors by endogenous DA is necessary for the normal persistence of tetanically activated LTP in area CA1, but not in the dentate gyrus.

Comparison of D₁/D₅ and β -adrenergic receptor activation on persistence of long-term potentiation in CA1 in vitro

Although we have observed a double dissociation of catecholamine effects on persistence of LTP across hippocampal subregions, these findings might simply reflect that the stimulation in CA1 selectively co-activated dopaminergic fibres, while the stimulation in the dentate gyrus selectively activated noradrenergic fibres. It has been shown, for example, that pharmacological activation of β -adrenergic receptors exerts profound effects on the membrane properties of CA1 pyramidal cells and lowers the threshold for LTP.^{28,37} Thus, it might be that if noradrenergic synapses are sufficiently activated during the tetanus, they would contribute to persistence of LTP in CA1.

To test this possibility, we returned to the slice preparation which offers good temporal control of drug administration, and administered either the β -adrenergic agonist isoproterenol (0.5 μ M), a dose known to potentially increase pyramidal cell

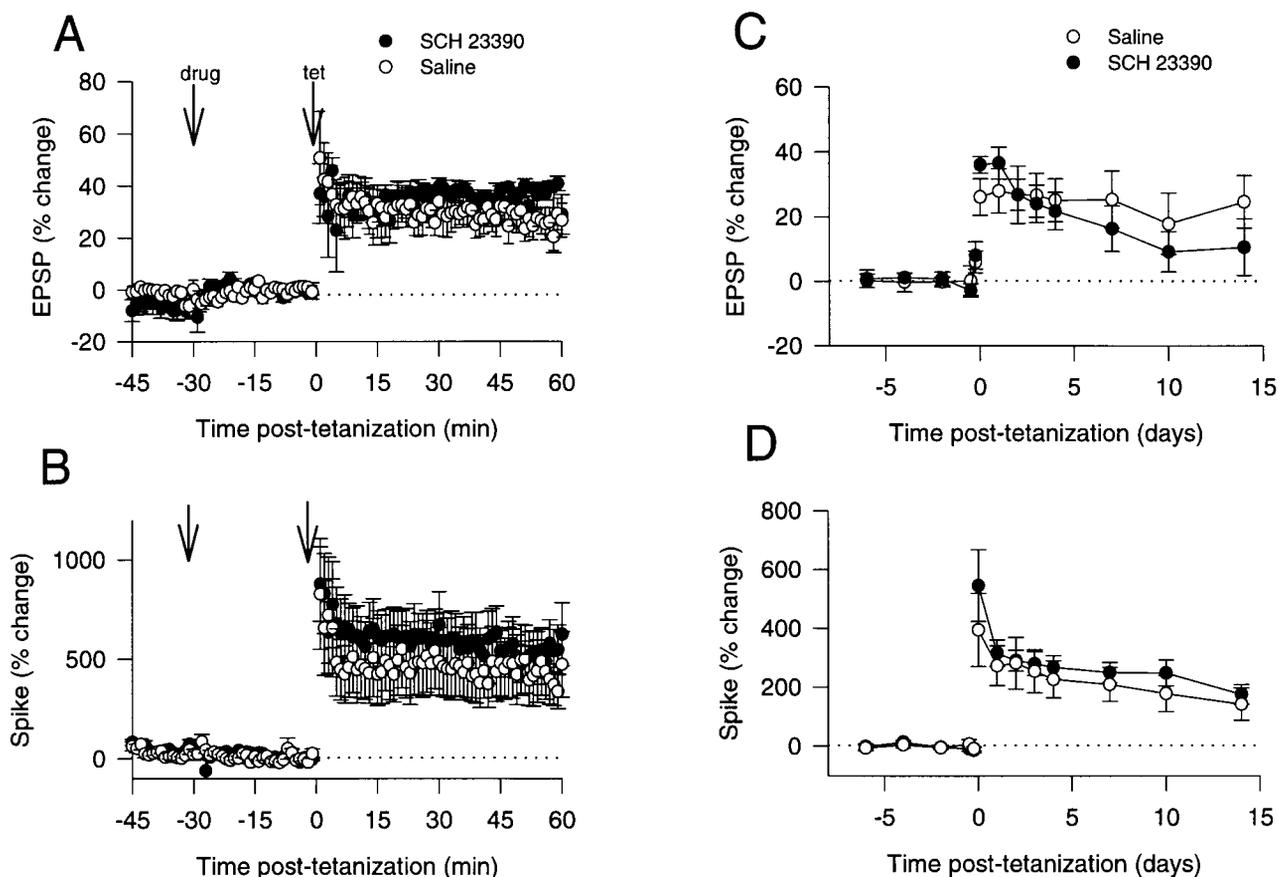


Fig. 5. Lack of effect of SCH-23390 on induction and persistence of LTP in the dentate gyrus *in vivo*. SCH-23390 (5 mg/kg, left-hand arrow) was injected 30 min prior to high-frequency stimulation (tet, right-hand arrow). There was no effect of the drug on basal synaptic transmission nor on LTP induction for either the EPSP (A) or the population spike (B). LTP decay for the two weeks post-tetanus was also generally unaffected by the drug treatment (C, D).

excitability,²¹ or the D₁/D₅ receptor agonist SKF-38393 (150 μ M) during LTP induction in area CA1. For these experiments, a weak tetanus protocol was employed (five bursts of pulses, five pulses per burst at 100 Hz, 200 ms between bursts), which in control slices elicited a rapidly decaying form of LTP that in controls registered only $17 \pm 8\%$ ($n=4$) 1 h post-tetanus (Fig. 7A). Administration of isoproterenol for 10 min prior to and during the tetanus resulted in a marked increase in the initial induction of LTP, but by 1 h post-tetanus this LTP was not significantly greater than the controls ($28 \pm 4\%$, $n=5$). When the decay of LTP was fit by a double exponential function for each slice, it was clear that the decay time constant of the second exponential for drug-treated slices was less (i.e. showed faster decay) than that observed for controls (mean control slow time constant = 94 min; isoproterenol slow time constant = 50 min), although this effect was not statistically significant. Similar results were found using a 20-min application of isoproterenol (data not shown).

The effect of SKF-38393 on CA1 LTP contrasted markedly with that observed for isoproterenol.

SKF-38393 had no effect on the initial induction of LTP, but the LTP induced persisted significantly longer over a 3-h period (Fig. 7B). The amount of LTP remaining 3 h post-tetanus was $18 \pm 4\%$ ($n=6$) in drug-treated slices compared to $4 \pm 4\%$ ($n=5$) in control slices. Since it has been reported that SKF-38393 can, by itself, induce a slow-onset potentiation in CA1 slices,²³ we conducted control experiments to determine whether such an effect could account for the apparent drug effect on LTP observed above. Slices given SKF-38393 for the same period of time as above (20 min) but not given tetanization showed no slow-onset potentiation under our conditions (EPSP 3 h post-drug: $-10 \pm 3\%$, $n=3$; Fig. 7B). Thus, the facilitation of LTP persistence in the drug-treated slices was not due simply to the drug treatment alone.

In summary, the data from these latter experiments confirm that the persistence of LTP in area CA1 is under the selective regulation of DA, as pharmacological activation of β -adrenergic receptors failed to prolong LTP. These findings stand in contrast to the potent regulation of LTP in the dentate gyrus by β -adrenergic receptor activation.^{14,42}

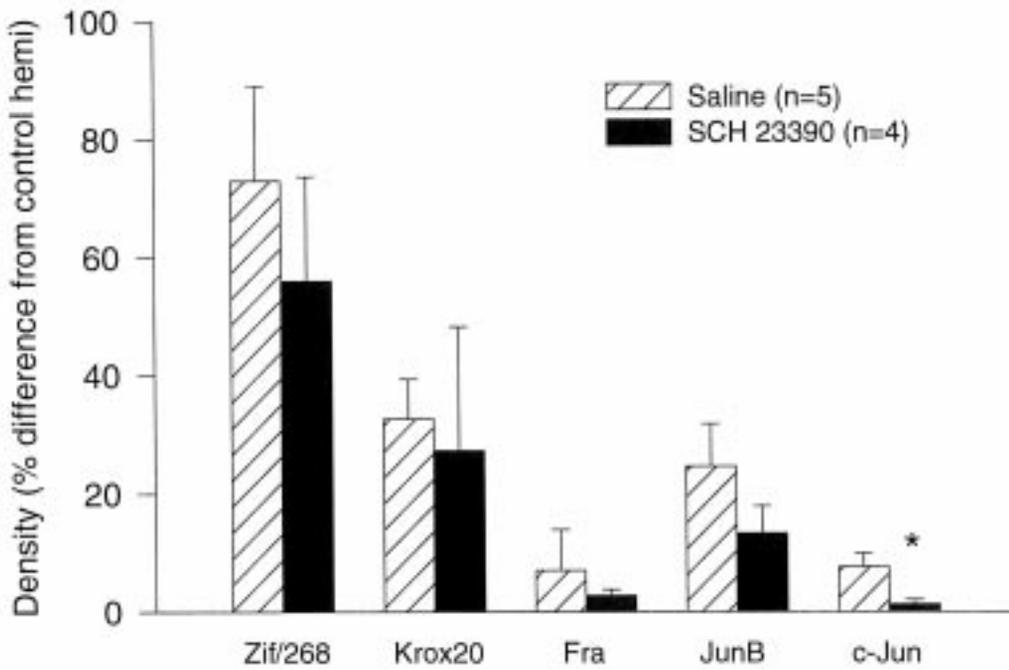
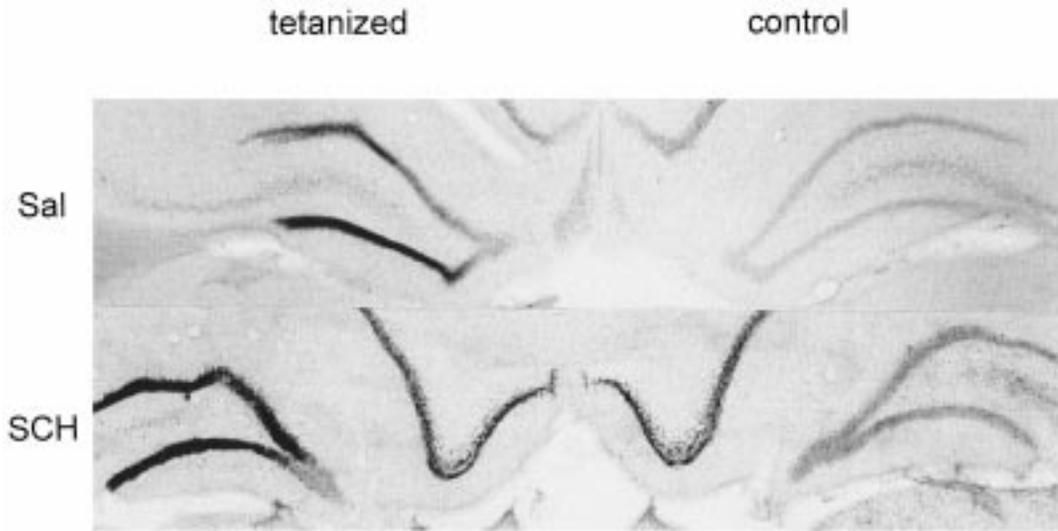


Fig. 6. Immunohistochemical analysis of the expression of various ITF proteins measured 1 h following LTP induction in the dentate gyrus. Top: induction of Krox 24 in the dentate gyrus granule cell layer ipsilateral (left side) to perforant path tetanization. There was a marked induction of Krox 24 1 h post-tetanization for both a saline-treated animal (Sal) and an SCH-23390-treated animal (SCH). Note the strong induction of Krox 24 in the granule cell layer of the tetanized hemisphere of both animals. Bottom: histogram comparing the ITF protein densities measured in the dentate gyrus granule cell layer for saline-treated and SCH-23390-treated (30 min pre-tetanus injection) animals. ITF protein induction was slightly reduced by SCH-23390, but only c-Jun showed a statistically significant decrease. * $P < 0.05$, Student's *t*-test. Data are mean \pm S.E.M. density expressed as percentage change from the control, non-tetanized hemisphere.

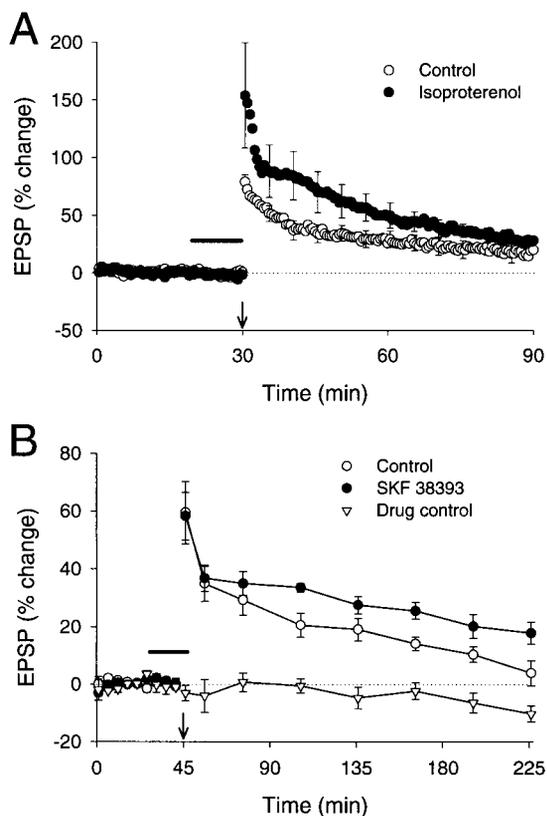


Fig. 7. D_1/D_5 but not β -adrenergic receptor activation enhances the persistence of LTP in CA1 *in vitro*. (A) Plot of mean percentage change in field EPSP slope in control and isoproterenol-treated slices before and after a weak tetanus (arrow). The initial induction of LTP was strongly enhanced by isoproterenol, but it decayed back to control levels within 60 min. (B) Mean percentage change in EPSP slope for control tetanized slices, slices tetanized in the presence of SKF-38393 (150 μ M) and non-tetanized slices exposed to SKF-38393. Induction of LTP was not affected by SKF-38393, but the LTP persisted significantly longer over a 3-h period. SKF-38393 alone had no effect on basal synaptic transmission (drug control). Bar indicates the time of drug application.

DISCUSSION

Double dissociation of catecholamine regulation of persistence of long-term potentiation

The data presented here demonstrate for the first time a regional double dissociation in the way that the catecholamines DA and NA regulate persistence of LTP in the hippocampus. D_1/D_5 but not β -adrenergic receptor activation is crucial for consolidating LTP in area CA1, while the converse is true for the dentate gyrus.

Considering the DA effects in more detail first, our data in CA1 have confirmed the findings of several previous reports that D_1/D_5 receptor activation is critical for the establishment of the protein synthesis-dependent phase of LTP in this brain region *in vitro*.^{17,23,30} This conclusion is now considerably strengthened by the new findings that a D_1/D_5 agonist facilitated the persistence of a weakly induced LTP in slices, and that DA receptor

activation was also necessary for LTP consolidation in CA1 in awake animals. This latter result demonstrates that the necessity for DA is not an artifact of the slice preparation, and that even within the normal brain milieu D_1/D_5 receptor activation is crucial for LTP consolidation.

Whether D_1/D_5 receptors contribute to persistence of LTP in the dentate gyrus has not been investigated previously. Mixed findings have been reported regarding their contribution to induction of LTP,^{26,48} but in our hands there was no effect of SCH-23390 on induction of LTP in either slices or awake animals. More importantly for this study, we also did not observe any effects of the drug on persistence of LTP in either preparation, even though we tested a number of different protocols and for periods up to two weeks post-tetanus in awake animals. Furthermore, we did not observe any major effect of SCH-23390 on tetanization-induced ITF expression in dentate granule cells, which contrasts with its ability to block basal ITF expression in the striatum.²⁹ It remains to be seen, however, whether DA can exert an effect on persistence of LTP or ITF expression when receptor activation is ensured by pharmacological treatments. Nonetheless, our data at a minimum clearly show that D_1/D_5 receptor activation is not necessary for the consolidation of LTP in the dentate gyrus.

NA has long been known to play an important role in LTP induction in the dentate gyrus, as β -adrenergic receptor antagonists have been consistently shown to reduce induction of LTP in both medial and lateral perforant path synapses^{9,11,41} (but see Ref. 36). Our findings have confirmed these effects, and shown that both the induction of LTP and its persistence over 3 h are markedly reduced by propranolol. We were curious to ascertain, however, whether this requirement for NA extended to CA1. In previous studies, β -adrenergic antagonists have not affected LTP induction,¹⁵ but their effects on persistence of LTP have not been investigated. Our findings confirmed that propranolol has little effect on induction of LTP in CA1, and further demonstrated that, unlike SCH-23390, it also has no effect on persistence of LTP over a 3-h period. Induction of LTP at threshold can be markedly enhanced by β -adrenergic receptor activation,³⁷ but this enhanced LTP decayed as rapidly, if not more so, than controls (present results). Taken together, these data indicate that not only is there a double dissociation of effects on LTP persistence between NA and DA across hippocampal subregions, but there may also be a differential regulation by these catecholamines on the various temporal phases of LTP within CA1. Thus, β -adrenergic receptor activation strongly modulates the early induction phase of LTP in CA1^{33,37} (and present results), while D_1/D_5 receptor activation has variable, but at best only mild, effects on LTP induction^{18,32} (and present results). In

contrast, D₁/D₅ receptors potentially regulate the late phase(s) of LTP.

Mechanism for the catecholamine double dissociation

The differential effects of D₁/D₅ and β -adrenergic receptor activation are somewhat surprising, given that both receptor subtypes are coupled to stimulatory G-proteins that activate adenylyl cyclase and increase levels of cyclic-AMP. Furthermore, the two receptor subtypes are found in both CA1 and the dentate gyrus, and can affect cellular functioning in both hippocampal areas. One explanation for the differential regional effects is that the stimulation protocols or electrode placements managed to selectively activate only one population of catecholaminergic fibres in each subregion. However, this is unlikely to account for the differential effects, at least in CA1, since even pharmacological activation of the two receptor types produced differential effects on induction and persistence of LTP.

Another explanation may lie in the spatial distribution of D₁/D₅ receptors relative to the β -adrenergic receptors. D₁/D₅ receptors appear to be preferentially located on the spine necks near to the Schaffer collateral synapses,⁶ while β -adrenergic receptors cluster more on the pyramidal cell bodies and proximal dendrites or in the CA1 molecular layer.⁴⁵ It has been suggested that calcium-activated potassium channels may gate the induction of LTP, by controlling the level of membrane depolarization.³⁷ Since these channels are heavily located on proximal dendritic shafts, the β -adrenergic receptors are well positioned to regulate them,⁴⁵ and thereby the induction of LTP. The DA receptors, by being more clearly associated with specific synapses, may play a more prominent role in establishing local changes that promote the consolidation of synapse-specific LTP, even though DA can also regulate potassium channels³⁵ and weakly modulate LTP induction.³²

The reason for the differential regulation of LTP by DA and NA in the dentate gyrus is less clear. Both catecholamines are known to regulate the excitability of granule cells,^{46,48} and they appear to have similar terminal and receptor distributions, with a dense innervation of the dentate hilus just subjacent to the granule cell layer, together with a more sparse innervation of the outer half of the molecular layer.⁴³ β -Adrenergic receptor activation increases voltage-dependent calcium channel activity in the dentate gyrus,¹⁹ but it is not known whether this also occurs in area CA1. Another possibility is that there are differences in the coupling of the receptor subtypes to pre- or postsynaptic biochemical cascades. It has been shown, for example, that β -adrenergic receptor activation triggers synapsin phosphorylation in the dentate gyrus, but not in area CA1.³⁴ DA receptors may thus couple

differentially to second messenger systems on a regional basis as well.

D₁/D₅ receptor-mediated induction of the late phase of long-term potentiation

One interesting aspect of the present findings is that administration of the D₁/D₅ receptor agonist SKF-38393, even at a relatively high dose, had no effect on baseline evoked potentials over a 3-h period. It has been reported previously that this treatment induces a protein synthesis-dependent slow-onset potentiation that occludes the subsequent induction of tetanically evoked LTP.²³ There are at least three major methodological differences that could account for this discrepancy. First, our slice experiments were performed on eight- to 12-week-old rats, while the previous studies were typically performed on younger animals. Second, unlike the prior studies, area CA3 was routinely removed from our slices. Finally, the levels of potassium ions in the bathing solution were higher in the previous experiments than in the present study. The latter two differences, at least, have been shown to be important contributing factors to the success of two other forms of slow-onset potentiation, metabotropic glutamate receptor LTP and calcium-induced LTP, respectively.^{10,20} These differences may affect the ease with which presynaptic cell bodies or terminals are activated by DA receptor activation, and may therefore indicate that postsynaptic mechanisms alone cannot account for the potentiation process.

Behavioural significance of the regional variation in the catecholaminergic control of long-term potentiation

The consolidation of LTP is powerfully regulated by NA in both the dentate gyrus (e.g., present results) and CA3, at least for the mossy fibre synapses,^{22,24} yet DA plays this role in CA1. What is the behavioural significance of this dissociation? While it is difficult to completely characterize their repertoire of responding in behaving animals, it is noteworthy that neurons in the locus coeruleus, source of the NA innervation of the hippocampus, are phasically activated by both noxious and non-noxious stimuli.⁴ They are also tonically inhibited during slow-wave sleep, but show marked activation just prior to waking.³ For these and other reasons, the locus coeruleus has often been described as participating in behavioural arousal as well as orienting responses and attention,²⁻⁴ through its divergent modulation of multiple brain regions. Dopaminergic neurons in the ventral midbrain, on the other hand, are typically activated during the expectation or receipt of positive reward.^{27,39} These differences in neural responses to behavioural stimuli suggest that consolidation of LTP, and to some extent its induction, may show regional

variations in its sensitivity to the behavioural state of the animals.

It has been suggested that, during exploration and initial learning, there is selective activation of the entorhinal–dentate–CA3 pathway, during which selective synaptic modifications may occur. Modification of these pathways would be turned off during later behaviourally quiet periods or slow-wave sleep.¹³ This fits well with the noradrenergic control of dentate gyrus and CA3 LTP, since these periods of learning correspond well with the behavioural situations when locus coeruleus neurons are active. Conversely, it has been observed that, during behaviourally quiet periods, slow-wave sleep and consummatory behaviours, there are sporadic bursts of activity in CA3 that phasically drive CA1 neurons (sharp waves),¹² and this may reflect the read-out of CA3-localized memory back through CA1 to the cortex for consolidation purposes.^{13,31} During periods of reward consummation, therefore, there may be a conjunction of dopaminergic activity and synaptic activity in CA1 and perhaps other limbic cortical areas, promoting the induction and consolidation of plasticity in these brain areas.

It is noteworthy, however, that endogenous catecholamines can influence persistence of LTP in hippocampal slices, which are cut off from the influences of afferent activity originating extrinsically to the hippocampus. Thus, endogenous catecholamines can affect LTP independently of behavioural state. This could simply reflect there being a constitutive release of catecholamines in slices, or that catecholaminergic fibres are being directly stimulated during the experiments. Another more intriguing possibility, however, is that the catecholamine release is locally controlled by glutamate released at activated synapses. There is evidence that glutamate can facilitate catecholamine release from synaptosomes via presynaptic glutamate receptors on catecholaminergic terminals,⁴⁶ and there may be sufficient extrasynaptic spillover

of glutamate during high-frequency stimulation to activate these receptors *in situ*.⁷ Alternatively, a mobile trans-synaptic messenger such as nitric oxide could serve a similar function. The finding that tetanization-induced cyclic-AMP accumulation in CA1 is blocked by both SCH-23390 and an NMDA receptor antagonist supports this latter possibility.¹⁶ If either of these scenarios were the case, then endogenous high-frequency activity in the hippocampus may have the capacity to be self-reinforcing, regardless of the activity state of the catecholamine cell bodies. This would provide a means for promoting the local consolidation of LTP, specific to the region of the activated synapses, without requiring a flood of catecholamine release throughout widespread regions of the brain that would be initiated by ventral tegmental area or locus coeruleus activity.

CONCLUSIONS

Our results have demonstrated a double dissociation of the catecholaminergic control of persistence of LTP between area CA1 and the dentate gyrus of the hippocampus. NA plays a privileged role promoting the late phase of LTP in the dentate gyrus, while DA fulfils that role in area CA1. Our findings are most complete for the *in vitro* preparation, and are indicative that the same functions are fulfilled by DA *in vivo*. Recent data have confirmed that NA plays a vital role in persistence of LTP in the dentate gyrus *in vivo*.⁴⁰ Overall, these data suggest that LTP in these brain areas may be differentially consolidated according to the animal's behavioural state.

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