The 5-Hydroxytryptamine<sub>4</sub> Receptor Exhibits Frequency-dependent Properties in Synaptic Plasticity and Behavioural Metaplasticity in the Hippocampal CA1 Region In vivo

Long-term plasticity, in the forms of long-term depression (LTD) and long-term potentiation (LTP), of synaptic transmission are thought to underlie memory. Biogenic amino acids modulate the expression of LTD and LTP. The serotonergic 5-hydroxytryptamine<sub>4</sub> (5-HT<sub>4</sub>) receptor has been shown to influence learning and memory. However, little is known about the role of this receptor in synaptic plasticity. Here we show that although induction of LTP is unaffected by either pharmacological activation or inhibition of 5-HT<sub>4</sub>, application of the 5-HT<sub>4</sub> receptor agonist, RS67333, completely blocks learning-induced depotentiation of LTP in the hippocampal CA1 region of freely moving rats, suggesting a role for 5-HT<sub>4</sub> receptors in behavioural metaplasticity. In addition, the 5-HT<sub>4</sub> antagonist RS39604 enhances the intermediate phase of LTD and converts short-term depression into persistent LTD (>24 h), suggesting a significant role for 5-HT<sub>4</sub> receptors in the expression of LTD in CA1. Stimulation at 10 Hz causes transient synaptic depression. However, 5-HT<sub>4</sub> antagonist application prior to 10 Hz stimulation leads to LTD, whereas agonist application leads to LTP expression. 5-HT<sub>4</sub> receptors thus shift the frequency–response relationship for induction of plasticity. Together, these findings suggest a key role for 5-HT<sub>4</sub> receptors in the regulation of synaptic plasticity and the determination of the particular properties of stored synaptic information.

Keywords: hippocampus, LTD, LTP, novelty-exploration, RS39604, RS67333

Introduction

Information storage most likely requires some form of synaptic plasticity (Martin et al., 2000). Both long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission are cellular models for synaptic plasticity which may work in cooperation during memory formation (Bear, 1996). Metaplasticity, defined as a higher order plasticity, reflects how the prior experience of a synapse may alter the subsequent ability of a synapse to modify its synaptic strength in response to a plasticity-inducing impulse (Abraham and Bear, 1996). The prior activation of NMDA (Mockett et al., 2002) or metabotropic glutamate receptors (Manahan-Vaughan et al., 1996), the history of electrical activity of a synapse (Wang and Wagner, 1999) and the behavioural state of an animal (Manahan-Vaughan and Brauneewell, 1999) all can strongly influence the subsequent expression of synaptic plasticity. However, little is known about how these processes may be influenced by different neuromodulators.

Serotonin is significantly involved in cognitive function (Buhot, 1997). The serotonin receptors are subdivided into seven types, 5-hydroxytryptamine<sub>1</sub>–<sub>7</sub> (5-HT<sub>1</sub>–<sub>7</sub>) (Barnes and Sharp, 1999). Except for the 5-HT<sub>1</sub> receptor, they are all G-protein-coupled receptors. Of particular interest from a cognitive point of view is the 5-HT<sub>4</sub> receptor. Together with 5-HT<sub>6</sub> and 5-HT<sub>7</sub>, the 5-HT<sub>4</sub> receptor belongs to the subfamily of serotonin receptors that are positively coupled to protein kinase A (PKA) via cAMP (Eglen et al., 1995).

Activation of 5-HT<sub>4</sub> enhances neuronal excitability (Ansanay et al., 1995; Bockaert et al., 1998). The 5-HT<sub>4</sub> receptors are widely expressed in the mammalian brain (Ulmer et al., 1996; Vilaro et al., 1996; Waeber et al., 1996), with strong expression occurring in the hippocampus, a structure particularly important for learning and memory. A number of reports indicate that 5-HT<sub>4</sub> receptors are involved in learning processes. For instance, 5-HT<sub>4</sub> agonists improve object and place recognition tested in a Y-maze (Lamirault and Simon, 2001). Acquisition of the platform position in the water maze is enhanced after 5-HT<sub>4</sub> application (Lelong et al., 2001). In monkeys the learning of a delayed-match-to-sample task is improved when a 5-HT<sub>4</sub> receptor agonist is given before the test (Terry et al., 1998). 5-HT<sub>4</sub> receptor agonists also counteract memory impairments induced by scopolamine or atropine (Fontana et al., 1997; Letty et al., 1997; Moser et al., 2002). Furthermore, in humans, it has been observed that patients suffering from Alzheimer’s disease undergo a substantial loss of 5-HT<sub>4</sub> receptors in the hippocampus (Reynolds et al., 1995).

Whereas no independent effects of 5-HT<sub>4</sub> antagonists occurred in the above-mentioned studies, one study has shown that antagonists can interfere with olfactory associative memory (Marchetti et al., 2000). This indicates that the 5-HT<sub>4</sub> receptors are more significantly involved in some forms of memory than in others.

A receptor that influences both neuroexcitability and cognitive functions, and furthermore is located in areas participating in learning and memory processes, seems to be a likely candidate for modulation of synaptic plasticity. However, the role of 5-HT<sub>4</sub> receptors in synaptic plasticity is not well characterized. In the dentate gyrus it has been shown that 5-HT<sub>4</sub> receptor activation inhibits LTP in concentrations that also have an inhibitory influence on basal synaptic transmission. On the other hand, agonists elicited a detrimental effect on depotentiation of LTP in concentrations which did not affect basal synaptic transmission (Kulla and Manahan-Vaughan, 2001). In the CA1 region, 5-HT<sub>4</sub> receptor activation prevents learning-induced facilitation of LTD (Kemp and Manahan-Vaughan, 2004). In light of this intriguing finding, the aim of this study was to investigate the role of 5-HT<sub>4</sub> receptors in induction and expression of synaptic plasticity in CA1 of freely moving animals.

Materials and Methods

Electrophysiology

Male Wistar rats (7–8 weeks, Harlan Winkelmann or Charles River, Germany) underwent hippocampal implantation of a recording
electrode into the CA1 stratum radiatum, a bipolar stimulation electrode into the Schaffer collateral pathway and a guide cannula into the ipsilateral cerebral ventricle (icv), as described previously (Manahan-Vaughan, 1997). During experiments (commenced after 7–10 days of recovery from surgery), animals had free access to food and water and could move freely in a recording chamber (40 x 40 cm). To evoke field excitatory postsynaptic potentials (fEPSPs) a biphasic stimulus was given with a half-wave duration of 0.2 ms. Recordings were made with a stimulus strength which evoked an fEPSP which was 40% of the maximum observed during acquisition of an input–output (i/o) relationship (100–900 μA). The slope of the five steepest points on the first negative deflection of the fEPSP was used for analysis. Test-pulse stimulation was given at a frequency of 0.025 Hz, and for each time-point an average of five consecutive evoked responses was made. To ensure that the potentials were stable, baseline recordings were made with all animals at least 24 h before experiments were conducted. Low-frequency stimulation (LFS) (900 pulses, 1 Hz) using a stimulation intensity which produced 70% of maximal fEPSP slope seen during the i/o analysis was given to induce LTD. To induce short-term depression (STD) a submaximal LFS was applied (700 pulses at 1 Hz, stimulus intensity at 70% of maximum i/o responses). In animals that were a minimum of 12 weeks old, LTD was evoked using a high-frequency tetanus (HFT) consisting of four bursts of 100 pulses at 100 Hz, with an interburst interval of 5 min, or 10 Hz (450 pulses) stimulation was applied. HFT or 10 Hz stimulation in younger animals caused epileptiform seizures.

**Novelty Exploration**

For studies of learning-induced plasticity, 30 min after injection, a holeboard, containing objects, was inserted into the recording chamber as described previously (Kemp and Manahan-Vaughan, 2004). HFT consisting of four bursts of 100 pulses at 100 Hz, with an interburst interval of 5 min, was given. The holeboard was removed immediately after HFT.

**Compounds and Drug Treatment**

The 5-HT4 receptor agonist RS67333 and the 5-HT4 receptor antagonist RS39604 (Biotrend, Germany) were dissolved in double-distilled water. A 5 μl volume was injected through an injection cannula inserted into the icv guide cannula over a 5 min period. (The injection cannula was inserted 5 min before injections began). Animals which served as controls received a vehicle injection of 0.9% NaCl. Injections were given 

**Data Analysis and Statistics**

For each time-point an average was made of five consecutive evoked responses. Recordings were taken every 5 min until 30 min after HFT or LFS (or injection in the case of baseline studies), then at 15 min intervals until 4 h had elapsed. After 24 h, an additional five recordings were made. The first 30 min of recordings were averaged, and served as the baseline. All data were expressed as mean percentage ± SEM of the baseline. Statistical evaluations were performed by analysis of variance (ANOVA). Ad-hoc Student’s t-tests were used for individual time-point differences. The level of significance was set at P < 0.05.

**Results**

**The Synaptic Response to Low Frequency Stimulation is Altered by Manipulation of 5-HT4 Receptors**

We investigated whether prior activation of 5-HT4 receptors influenced expression of LTD. Drug concentrations were sought that had no independent effects on basal synaptic transmission. Application of 7.5–50 μg of the 5-HT4 agonist RS67333 (n = 4–7) did not alter basal synaptic transmission (data not shown). When LFS at 1 Hz was given in the presence of 0.9% NaCl (n = 8), an enduring long-lasting (>24 h) depression of evoked fEPSPs was observed (Fig. 1). When LFS was given in the presence of RS67333 (25 μg), the initial response was similar to the depression observed in vehicle-group (t = 5 min post-LFS, 69.1 ± 6.8 versus 67.9 ± 4.2% in vehicle-treated group). There was, however, a rapid increase in response magnitude and 30 min after LFS, where fEPSP values reached 90.6 ± 3.0%. Responses persisted at this level until at least 24 h post-LFS.

ANOVA revealed an overall significance in drug-effects $F(1,24) = 164.9, P < 0.0001; n = 8$, and t-tests revealed significant differences of the individual time-points from t = 30 min ($P < 0.05$). With a lower concentration (10 μg) of RS67333 we observed a similar block of LTD [$F(1,24) = 137.7, P < 0.0001; n = 8$]. There was no significant difference in the effectiveness of inhibiting the expression of LTD between the two drug-groups [$F(1,24) = 0.21, P = 0.644; n = 8$].

We then investigated the effect of 5-HT4 receptor antagonism on LTD. Application of the 5-HT4 antagonist RS39604 (25–50 μg, n = 4) did not alter basal synaptic transmission (data not shown). Application of 25 μg RS39604 did not change the profile of LTD (Fig. 2a; ANOVA: $F(1,24) = 0.14, P = 0.154$, compared with controls (n = 4)). The fEPSP slope values at 5 min, 4 and 24 h were 70.9 ± 4.9, 85.8 ± 3.5 and 78.0 ± 5.8% respectively (data not shown). On the other hand, the higher concentration of 50 μg of RS39604 elicited an overall enhancement of LTD [ANOVA: $F(1,24) = 19.91, P < 0.0001( n = 7 in both groups)]).

Likewise, there was no difference in the expression of the late phase of LTD. However, the intermediate phase of LTD showed a delayed decay before the potentials stabilized in the depressed state. This became evident at 90 min after LFS, when fEPSP values were 79.1 ± 4.4% in the vehicle-treated group compared with 68.7 ± 2.1% after application of RS39604 ($P < 0.05$, t-test). After 180 min there was no longer any statistically significant differences between the two groups.

This finding prompted the question as to whether a weaker LTD could be enhanced by the antagonist. We therefore used a submaximal LFS (subLFS) consisting of 700 pulses at 1 Hz (Fig. 2b) to elicit STD in control animals. This protocol produced an initial depression in controls which was no different from that observed after 900 pulses were applied ($P > 0.05$, t-test), but 60 min after application of subLFS, fEPSP values had returned to levels that were not statistically different from test-pulse recordings in control animals ($P > 0.05$, t-test). Application of RS39604 (50 μg) prior to subLFS resulted in conversion of STD into robust LTD (>24 h) [ANOVA: $F(1,24) = 109.7, P < 0.0001( n = 9 in both groups)].
Thus, agonist activation of 5-HT$_4$ receptors block LTD in the CA1 region in vivo, whereas antagonist treatment enhances the intermediate phases of robust LTD and also facilitates STD into persistent LTD.

**LTP is not Influenced by 5-HT$_4$ Receptor Activation or Inhibition**

The observation that LTD is enhanced by antagonism of 5-HT$_4$ receptors, and impaired by agonists of 5-HT$_4$ receptors prompted the question as to whether a tight interplay between 5-HT$_4$ receptors and LTP also exists. We induced LTP by four trains of 100 pulses given with an HFT of 100 Hz (5 min inter-train interval). Following this tetanization protocol, a robust LTP was observed that lasted for at least 24 h. As LTD was affected by both 10 and 25 µg of the 5-HT$_4$ receptor agonist RS67333, the same two concentrations were used in the LTP experiments (Fig. 3a). However, when either 10 µg ($n = 7$) or 25 µg ($n = 9$) RS67333 was injected before HFT, no significant change in the profile of LTD was observed (Fig. 3a) (confirmed by ANOVA).

The 5-HT$_4$ antagonist RS39604, in the higher concentration of 50 µg, elicited a facilitation of the intermediate phase of LTD, and conversion of STD into persistent LTD. Thus, neither the 5-HT$_4$ agonist nor antagonist, when applied in doses effective against LTD, influenced the expression of LTP induced by HFT. This suggests an exclusive regulation by 5-HT$_4$ receptors of LTD.

**Depotentiation Induced by Novelty Exploration is Prevented by 5-HT$_4$ Receptor Activation**

In a previous study we demonstrated that exposure of rats to an object-containing holeboard leads to depotentiation of LTP (Kemp and Manahan-Vaughan, 2004). The exploration of the holeboard is closely associated with learning (Manahan-Vaughan and Braunewell, 1999; Kemp and Manahan-Vaughan, 2004). Here, we investigated whether the 5-HT$_4$ receptor is involved in the regulation of this phenomenon.

When control animals were exposed to the holeboard, LTP was depotentiated (Fig. 4a, $n = 6$) [ANOVA: $F(1,24) = 101.81$, $P < 0.0001$]. Thus, 30 min after HFT a significant difference between animals that underwent HFT in the presence or absence of the holeboard occurred ($t$-test, $P = 0.022$) which was still evident 24 h post-HFT ($t$-test, $P = 0.008$). Prior injection of RS67333 significantly prevent learning-induced depotentiation (Fig. 4b). Thus, although 5-HT$_4$ activation does not alter the expression of electrically induced LTP, it prevents learning-induced depotentiation of LTP.
A 10 Hz stimulation, applied after injection of vehicle, resulted in a transient and weak depression (Fig. 5). After 45 min the fEPSPs had recovered to baseline levels ($t$-test; $P = 0.2160$, baseline compared with 10 Hz stimulation).

Injection of 50 µg of the 5-HT4 antagonist RS39604 converted the transient depression into robust LTD [ANOVA: $F(1,24) = 126.65$, $P < 0.0001$]. Twenty-four hours after the stimulus protocol, fEPSPs were 71.3 ± 6.5% of pre-LFS levels ($n = 7$) ($t$-test; $P = 0.0056$). Intriguingly, application of 10 µg of the 5-HT4 agonist RS67333 ($n = 7$) resulted in synaptic potentiation compared to vehicle injected controls ($n = 10$) [ANOVA: $F(1,24) = 102.05$, $P < 0.0001$]. Effects were significant from 135 min onwards ($t$-test; $P = 0.0321$).

**Discussion**

In the present study we found that pharmacological activation of 5-HT4 receptors inhibited LTD induced by LFS. In addition, antagonism of the 5-HT4 receptor prolonged the intermediate phases of robust LTD and converted STD into persistent LTD. Interestingly, the same drug concentrations that affected LTD had no effect on LTP, suggesting an exclusive role for 5-HT4 receptors in the regulation of LTD. However, activation of the 5-HT4 receptors prevented learning-induced depotentiation of LTD caused by exploration of an object-containing holeboard, suggesting a role for 5-HT4 receptors in behavioural metaplas ticity. Furthermore, activation of 5-HT4 receptors converted STD elicited by 10 Hz stimulation into significant synaptic potentiation, whereas antagonism of 5-HT4 receptors converted 10 Hz-elicited STD into LTD, supporting frequency-dependent properties of the 5-HT4 receptors in synaptic plasticity. These data emphasize a specific role for 5-HT4 receptors in metaplas ticity, highlight the significance of these receptors for LTD and indicate that 5-HT4 receptors shift the frequency-response relationship for induction of plasticity.

One of the most fascinating results obtained in this study was that pharmacological blockade of 5-HT4 receptors influenced expression of LTD, although no effect was seen on LTP. Robust LTD, induced by strong LFS, underwent a subtle enhancement of the intermediate phases of LTD expression, whereas short-term depression (induced by weak LFS) was facilitated into LTD by the same concentration of antagonist. Agonist application prevented LTD, whereas neither agonist or antagonist affected LTP. These results support a functionally exclusive role for 5-HT4 in LTD. Activation of the receptor may serve to veto persistent LTD expression, thus returning excessive LTD, or favouring the induction of LTD under specific conditions. The 5-HT4 receptor modulates LTD not directly, but by changing the crossover-point for LTD/LTP induction, and by preventing LTD it may permit a reduction of ‘noise’ and thus optimize LTD. Given the known role for LTD in spatial learning (Morris et al., 1986) and of LTD in novelty recognition (Manahan-Vaughan and Braunewell, 1999; Kemp and Manahan-Vaughan, 2004), these physiological conditions may arise when a purely spatial learning task is being acquired by the animal.

What could be the mechanism underlying this phenomenon? It has previously been observed that PKA activation inhibits LTD (Carvalho et al., 2000). AMPA receptor regulation comprises an important aspect of long-term changes of synaptic plasticity (Blackstone et al., 1994; Malinow and Malenka, 2002). Under naive synaptic conditions the receptor is phosphorylated by PKA, but after induction of LTD the AMPA receptor adopts...
a dephosphorylated state which renders it silent (Kameyama et al., 1998; Banke et al., 2000; Lee et al., 2000). Thus, after the pharmacological activation of 5-HT_{4} receptors, PKA may shift the equilibrium towards phosphorylation of the AMPA receptor and thereby, to the ‘naive’ functional state of the synapse. This could explain why LTD was not induced in the presence of 5-HT_{4} agonist. Two agonist concentrations were tested against LTD, and both concentrations blocked LTD to a similar degree. This suggests that receptor saturation was already achieved by the lower concentration of the agonist, or that a sufficient number of receptors were activated by the low concentration to enable an elevation of PKA to levels high enough to prevent dephosphorylation of GluR1.

Our findings with regard to the CA1 region are in contrast to an earlier study in the dentate gyrus of freely moving rats (Kulla and Manahan-Vaughan, 2001), where a critical role for 5-HT_{4} receptors in synaptic plasticity was excluded on the basis that antagonist (RS39604) application elicited no effects on either LTP or depotentiation. In contrast, in the present study, antagonism of 5-HT_{4} receptors enhanced electrically induced LTD but left LTD unaffected. This suggests that the 5-HT_{4} receptor may have a regional importance with regard to synaptic plasticity. It is not known which PKA isoforms are those activated by 5-HT_{4} receptors. It is known, however, that the 5-HT_{4} receptor exists in several different splice variants (Bender et al., 2000), and these differ in their signal transduction mechanism (Pindon et al., 2002). Different complements of isoforms may be expressed in the different hippocampal subregions, which could in turn explain the differences in synaptic plasticity regulation by 5-HT_{4} receptors seen in these studies.

In the present study, we found that activation of 5-HT_{4} receptors prevents both electrically induced LTD and behaviourally induced depotentiation of LTD. LTP was unaffected by agonist manipulation of 5-HT_{4} receptors. Interestingly, none of the concentrations of 5-HT_{4} receptor ligands which were effective in the dentate gyrus (Kulla and Manahan-Vaughan, 2001) were found to be effective in the CA1 region in the present study. It has been argued that electrically induced LTD and depotentiation may share common mechanisms (Wagner and Alger, 1996). On the other hand, our laboratory and others have provided evidence to the contrary (Fitzjohn et al., 1998; Kulla et al., 1999; Klausnitzer et al., 2004). It may be the case, however, that behaviourally induced depotentiation of LTP incorporates mechanisms common to behaviorally induced LTD: the behavioural stimulation (i.e. learning during holeboard exploration) used in this study to depotentiate HFT-induced LTP is identical to the behavioural protocol which facilitated LTD in a previous study (Kemp and Manahan-Vaughan, 2004). In both experiments 5-HT_{4} receptor activation inhibited the given type of plasticity. This suggests a common regulation of both behaviourally induced depotentiation and behaviorally induced LTD by the 5-HT_{4} receptor.

It has previously been reported that the 5-HT_{4} receptor agonist RS67333 facilitates potentiation of population spike amplitude in CA1 in vivo (Matsumoto et al., 2001). In the present study we focused on fEPSP recordings and found no potentiation of fEPSPs resulting from RS67333 application. This finding is not surprising in light of observations from in vitro studies, where, for example, it has been shown that application of zacopride (a 5-HT_{3} antagonist/5-HT_{4} agonist) enhances population spike amplitude recorded from the cell body layer in CA1, whereas no increase in fEPSP (recorded in stratum radiatum) was detected (Bijaq et al., 1997). Effects may also be region specific: in the dentate gyrus in vivo, the population spike amplitude was affected by lower agonist doses than those necessary to affect fEPSP slope (Kulla and Manahan-Vaughan, 2001). In the present study, given the fact that LTP occurs at the synapse and our measurements were taken at the level of the Schaffer collateral-stratum radiatum synapse, we can conclude that alterations of LTP expression did not occur following activation of 5-HT_{4} receptors. In this study we used a strong HFT which might induce a nearly saturated LTP in the CA1 region. Thus, one cannot exclude that facilitatory effects may have been masked by the powerful LTP induced; being only detected in situations where a weaker LTP is elicited.

Stimulation at 10 Hz is thought to lie at the threshold between LTD and LTP where neither form of plasticity is generated (Dudek and Bear, 1993; Coussens and Teyler, 1996). In our studies, we have found that whereas 1 Hz LFS elicits LTD and 100 Hz HFT elicits LTP, 10 Hz stimulation does not alter synaptic strength (Manahan-Vaughan, 2000). Stimulation at this frequency is therefore particularly suitable for examining a possible shift in the sliding threshold elicted by neurotransmitter modulation. In controls, 10Hz stimulation induced short-term depression. However, synaptic potentiation was observed when 10 Hz was given in the presence of a 5-HT_{4} receptor agonist. On the other hand, LTD was elicited by 10Hz stimulation in the presence of a 5-HT_{4} receptor antagonist. These findings suggest that the 5-HT_{4} receptor exhibits frequency-dependent properties, and thus regulates the sliding threshold of the BCM model and the direction of plasticity.

What are the implications of the findings of this study? The 5-HT_{4} receptor is involved in various forms of cognitive processes in the mammalian brain, particularly concerning different learning tasks (Fontana et al., 1997; Kennet et al., 1997; Marchetti-Gauthier et al., 1997; Meneses and Hong, 1997; Meneses, 1998; Terry et al., 1998; Lamirault and Simon,
consistent with a role of 5-HT4 receptors in both LTD and 5-HT4 receptors in regulating the type of information encoded. Prevents this depotentiation indicates a significant role for watermaze, which may involve LTP (Morris et al., 1986). 5-HT4 receptor agonists have a beneficial effect on acquisition (Fontana et al., 1997; Lelong et al., 2001).

Learning of object-place association is dependent upon induction of LTD (Kemp and Manahan-Vaughan, 2004). In accordance with our results and this functional role of LTD, 5-HT4 receptor activation would be expected to impair this type of learning. Tests of the relationship between object-place acquisition and facilitation of LTD (Kemp and Manahan-Vaughan, 2004) have revealed that the facilitation of LTD by object acquisition is indeed blocked by a 5-HT4 agonist. This is consistent with a role of 5-HT4 receptors in both LTD and object recognition. Based on our observations that exploration of novel empty holeboard favours LTP induction whereas exploration of novel objects in a holeboard not only favours LTD induction but also depotentiates LTP, we suggest that in the CA1 region the encoding of object-place relationships via LTD has a stronger impact than encoding of space by LTP. The finding that the activation of 5-HT4 receptors completely prevents this depotentiation indicates a significant role for 5-HT4 receptors in regulating the type of information encoded.

In conclusion, our data support a specific role for 5-HT4 receptors in regulating LTD in the hippocampal CA1 region. This regulation appears to function on the level of metaplasticity as our data indicate that 5-HT4 receptors shift the frequency–response relationship for induction of LTD and LTP. Although antagonists of the receptors enhance LTD, no effect on LTP is seen. However, agonist application causes a frequency response shift in favour of LTP, as well as the prevention of depotentiation induced by novelty exploration, although no direct effect on LTP is seen. Agonist application also prevents learning-induced facilitation of LTD. Taken together, these data suggest that synaptic stimulation in the presence of 5-HT4 receptor activation favours LTP indirectly, through suppressing LTD and LTD-associated learning mechanisms. This may lead, under specific conditions, to optimization of LTP and encoding of space in the CA1 region, at the expense of LTD and the encoding of spatial features.

Notes
This work was supported by grants from the Deutsche Forschungsgemeinschaft (SFB 515/B8 and SFB 509/B3) to DM-V. Address correspondence to Denise Manahan-Vaughan, Learning and Memory Research, International Graduate School for Neuroscience, Ruhr University Bochum, Universitätsstr. 150, 44780 Bochum, Germany. Email: vaughan@neurobiologie.rub.de.

References


