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8-Cyclopentyltheophylline, an adenosine A_1 receptor antagonist, inhibits the reversal of long-term potentiation in hippocampal CA1 neurons

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Abstract

The effects of an adenosine A_1 receptor antagonist, 8-cyclopentyltheophylline (8-CPT, 1 μM), on the reduction of long-term potentiation were studied in CA1 neurons of guinea pig hippocampal slices. Reduction of long-term potentiation (depotentiation) was achieved by delivering a train of low-frequency afferent stimuli (low-frequency stimulation, 1000 pulses, 1 Hz) 20 min after the tetanus (100 Hz, 100 pulses). In control experiments, low-frequency stimulation reduced the potentiated component of the slope of the field EPSP and the amplitude of the population spike by $68.5 \pm 14.4\%$ and $80.1 \pm 8.8\%$, respectively ($n = 6$); these values were significantly reduced to $13.4 \pm 9.7\%$ and $9.0 \pm 10.9\%$ ($n = 7$) when the low-frequency stimulation was applied during the perfusion with 8-CPT (1 μM). These results indicate that activation of adenosine A_1 receptors enhances the depotentiation of long-term potentiation. © 1997 Elsevier Science B.V.

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1. Introduction

Long-term potentiation is a state of persistent synaptic enhancement induced by a brief period of a high-frequency electrical stimulation (tetanus) of afferents (Bliss and Lømo, 1973; Bliss and Gardner-Medwin, 1973). In addition to long-term potentiation, another type of synaptic plasticity, 'depotentiation', has been reported, in which low-frequent afferent stimulation (low-frequency stimulation) effectively reverses a pre-established long-term potentiation, both in vivo (Barrioneuvo et al., 1980; Stäubli and Lynch, 1990) and in vitro (Fujii et al., 1991; Bashir and Collingridge, 1994; Stäubli and Lynch, 1996). These activity-dependent synaptic plasticities have been suggested to be responsible for important processes involved in the cellular basis of memory and learning (Collingridge, 1987; Collingridge and Bliss, 1987; Bliss and Collingridge, 1993).

During delivery of input stimulation to hippocampal CA1 neurons, a significant amount of ATP and adenosine derivatives is released from presynaptic terminals into the synaptic cleft in a frequency-dependent manner (White, 1978; Schubert et al., 1979; Wieraszko et al., 1989). In central nervous tissue, adenosine, acting via at least two major classes of adenosine receptors, A_1 and A_2 (Van Calker et al., 1975; Londos et al., 1980), modulates many physiological functions (Phillis et al., 1975; Snyder, 1985; Durcan and Morgan, 1989; Phillis, 1990). Activation of adenosine A_1 receptors inhibits adenylyl cyclase and thereby reduces cyclic AMP formation, while activation of adenosine A_2 receptors has the opposite effect (Fredholm et al., 1982; Dunwiddie and Fredholm, 1989; Lupica et al., 1990). In hippocampal neurons, endogenous adenosine and its derivatives, acting via adenosine A_1 and/or A_2 receptors, are therefore considered to be involved in the mechanism of the frequency-dependent synaptic plasticity, such as long-term potentiation and depotentiation of long-term potentiation.

Arai et al. (1990) have reported that adenosine, acting

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via adenosine A_1 receptors, interrupts long-term potentiation development in hippocampal CA1 neurons. Sekino et al. (1991) have shown that CP-66713, a potent adenosine A_2 receptor antagonist (Sarges et al., 1990), prevents long-term potentiation induction in terms of the evoked postsynaptic potential (EPSP), but has no effect on the amplitude of the population spike in CA1 neurons; they therefore suggested that endogenous adenosine, released by tetanic stimulation and acting via adenosine A_2 receptors, facilitates long-term potentiation induction in the EPSP but not in the population spike, leading to attenuation of the EPSP-PS dissociation (Taube and Schwartzkroin, 1986). In hippocampal CA1 neurons, CP-66713 is reported to facilitate depotentiation of long-term potentiation in the EPSP but inhibits it in the population spike, indicating that the action of endogenous adenosine in these mechanisms is via activation of adenosine A_2 receptors, leading to the attenuation of the EPSP-PS dissociation (Fujii et al., 1992). However, the role of the adenosine A_1 receptors in depotentiation of long-term potentiation has not been studied in detail.

In this report, we therefore perfused hippocampal slices with 8-cyclopentyltheophylline (8-CPT), a potent adenosine A_1 receptor antagonist (Bruns et al., 1980, Bruns et al., 1987), during the low-frequency stimulation and evaluated the effects on depotentiation of long-term potentiation.

2. Materials and methods

The techniques used in animal preparation, recording, stimulation, and data analysis were almost identical to those described previously (Fujii et al., 1991). In short, hippocampal slices (500 μm), prepared from adult male guinea pigs (300–400 g), were preincubated in a standard medium, consisting of (in mM): NaCl, 124; KCl, 5.0; NaH_2PO_4, 1.25; $MgSO_4$, 2.0; $CaCl_2$, 2.5; $NaHCO_3$, 22.0 and glucose, 10.0. in a 95% O_2 and 5% CO_2 atmosphere at 30–32°C for at least 1 h. A bipolar stimulating electrode (S, in Fig. 1A) was placed in the stratum radiatum to stimulate the input pathways to the CA1 neurons and

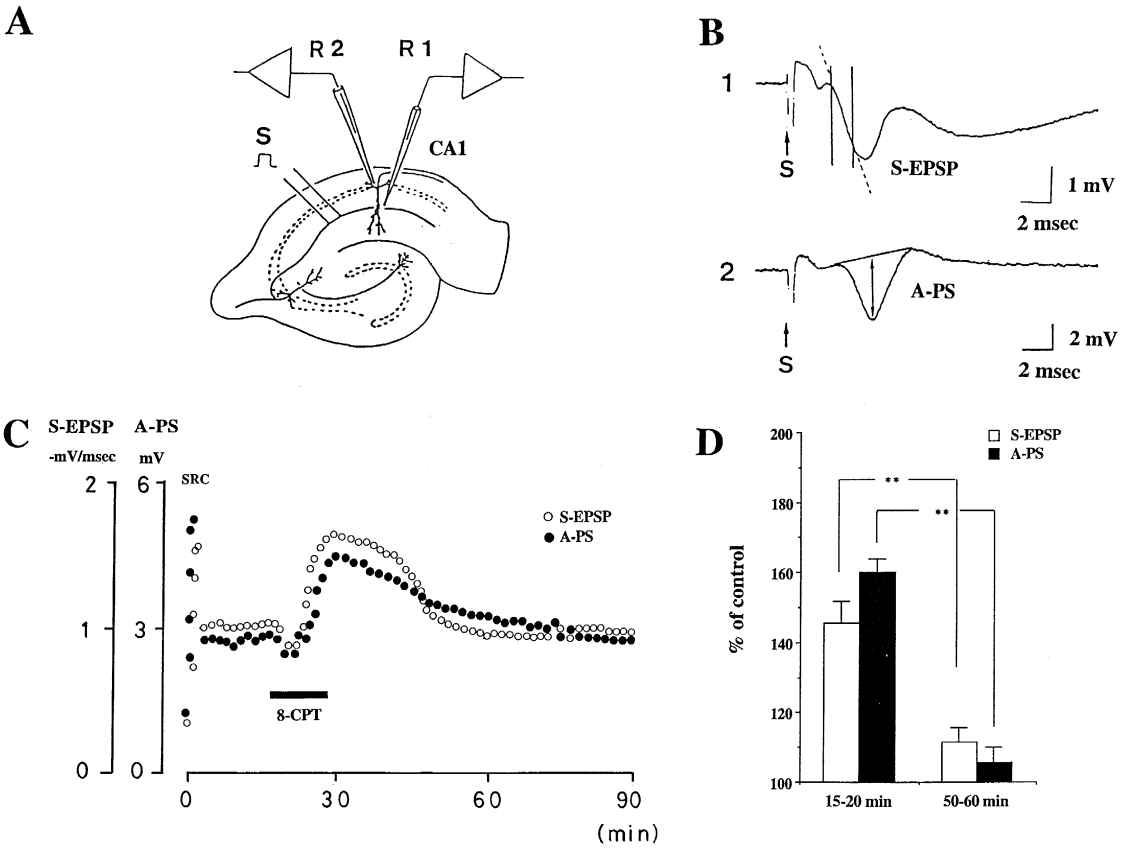

Fig. 1. (A) Schematic depiction of a hippocampal slice and the placement of a stimulating (S) and two recording electrodes (R1, R2). (B) Evoked responses recorded from the dendritic layer using electrode R1 (1) and from the pyramidal cell layer using R2 (2) and indicating parameters measured. S-EPSP, slope of EPSP; A-PS, amplitude of population spike; S, stimulus artifacts. (C) Effects of 8-CPT on responses. 8-CPT (1 μM) was applied (horizontal bar) to a naive slice with a test stimulus at 20-s intervals. The graph shows the S-EPSP (open circles) and the A-PS (filled circles); three successive responses were averaged and plotted. SRC indicates strength response curve recorded at the beginning of each experiment. (D) Averaged percentage change (+S.E.M.) in the S-EPSP and A-PS 15–20 and 50–60 min after the end of 8-CPT perfusion. ** Indicates a significant difference ($P < 0.01$) between the responses in the two periods.

recording electrodes positioned in both the pyramidal cell body layer (R_2) and in the stratum radiatum (R_1) of the CA1 region. At the beginning of each experiment, a stimulus/response curve (SRC in Fig. 1C and Fig. 2) was established by measuring the amplitude of the population spike (A-PS in Fig. $1B_2$). Based on the input/output function of the stimulus/response curve, the strength of the stimulus was adjusted to elicit a population spike with an amplitude 40–60% of the maximum. After checking the stability of the responses to a 20 s interval test stimulus, a tetanus (100 pulses at 100 Hz) was delivered to elicit long-term potentiation (T in Fig. 2C and D) followed, 20 min later, by a train of low-frequency afferent stimuli (1000 pulses at 1 Hz, low-frequency stimulation in Fig. 2) to eliminate the long-term potentiation. After low-frequency stimulation, the test stimulus was repeated every 20 s and responses were recorded for a minimum of 60 min. To evaluate the depotentiation of long-term potentiation in both the EPSP and the population spike, the slope of EPSP (S-EPSP in Fig. $1B_1$) and amplitude of the population spike were measured, using a microcomputer.

The changes in responses after the tetanus (long-term potentiation) and low-frequency stimulation (depotentiation of long-term potentiation) were calculated as follows (Fig. 2C): (1) the percentage change in response after tetanus, $(Y/X) \cdot 100$; (2) the percentage reduction in long-term potentiation after low-frequency stimulation, $((Y - Z)/(Y - X)) \cdot 100$ and (3) the percentage change in long-term potentiation response after low-frequency stimulation, $Z/Y \cdot 100$, where X is the averaged value for the 10 min just prior to tetanus; Y, the averaged value 15–20 min after tetanus and Z, the stable level 50–60 min after the low-frequency stimulation. For the equation given under (2), values of 100 and 0% indicate complete reduction to the pre-tetanic control level and no depotentiation of long-term potentiation by LFS, respectively. The equation given under (3) indicates the percentage reduction of response, with the pre-conditioning long-term potentiation being taken as 100%. 8-CPT (1 μM) was applied 5 min before low-frequency stimulation and was replaced by standard medium just after the end of the low-frequency stimulation.

In control experiments, direct effects of the antagonist on synaptic transmission in CA1 neurons were studied by adding 8-CPT (1 μM) to the perfusing medium for 10 min while delivering the test stimuli and its effect on responses after low-frequency stimulation studied by adding 8-CPT (1 μM) to the perfusing medium a few min before and during low-frequency stimulation.

All values are given as mean ± S.E.M. (%) and the

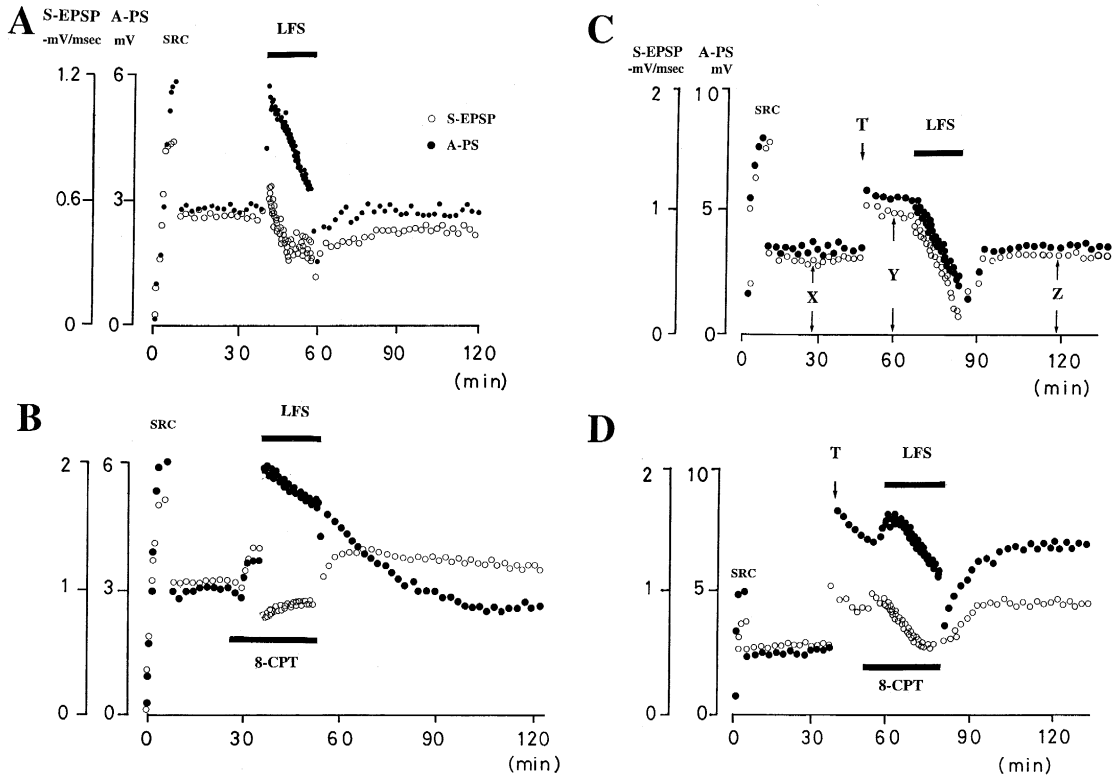

Fig. 2. Examples of responses of low-frequency stimulation (1 Hz, 1000 pulses, upper horizontal bar) applied to a naive slices (left panels) or 20 min after tetanus (T, 100 Hz, 100 pulses) (right panels) in the absence (A, C) and presence of 8-CPT (1 μM, lower horizontal bar) (B, D). Three successive responses were averaged and plotted: an open circle represents the slope of EPSP (S-EPSP) and a closed circles the amplitude of population spike (A-PS). SRC indicates the strength response curve recorded at the beginning of each experiment. X, Y and Z indicate the averaged response prior to tetanus (control level), 15–20 min after tetanus and 50–60 min after the end of low-frequency stimulation, respectively.

results were analyzed for statistical significance ($P < 0.05$ or $P < 0.01$) using Student's *t*-test (two tailed).

3. Results

Adenosine A_1 receptor antagonists are known to enhance the excitability of CA1 hippocampal neurons (Dunwiddie et al., 1981). In the present study, transiently increased responses were seen when 1 μM 8-CPT was applied for 10 min; these started to increase almost 5 min after beginning of 8-CPT perfusion and declined to the control level within 50–60 min. A typical example is shown in Fig. 1C. 15 to 20 min after wash-out of 8-CPT, the slope of EPSP and amplitude of population spike were $145.6 \pm 6.1\%$ and $160.0 \pm 8.3\%$ of the control level, respectively ($n = 7$); however, 50–60 min after removal of 8-CPT, these values were significantly ($P < 0.01$) reduced to $111.6 \pm 4.0\%$ and $105.7 \pm 4.3\%$ of the control level, respectively ($n = 7$, Fig. 1D).

Delivery of low-frequency stimulation (1 Hz, 1000 pulses) to a non-conditioned pathway induces a small long-term depression of responses; a typical example is shown in Fig. 2A. Just after low-frequency stimulation, the response to test stimuli was decreased in all cases; this was followed by recovery towards the control level, a plateau value being reached within a few min, or at most 45 min. The slope of EPSP and amplitude of population spike 50–60 min after the end of low-frequency stimulation were $92.5 \pm 4.9\%$ and $97.0 \pm 4.0\%$ ($n = 10$, Fig. 3, long-term depression) of control levels, respectively.

In contrast, a typical pattern of responses to low-frequency stimulation delivered to a non-conditioned pathway in the presence 1 μM 8-CPT is shown in Fig. 2B. In the presence of the antagonist, the slope of EPSP and amplitude of population spike 50–60 min after the end of low-frequency stimulation were $111.2 \pm 5.1\%$ and $93.3 \pm 6.6\%$, respectively ($n = 7$, Fig. 3, 8-CPT + LTD). 50–60 min after the low-frequency stimulation delivered in the presence of 1 μM 8-CPT, the slope of EPSP being significantly enhanced ($P < 0.05$) while the amplitude of population spike remained depressed (Fig. 3).

Long-term potentiation was induced in both the slope of EPSP and the amplitude of population spike by the delivery of the tetanus (100 Hz, 100 pulses). The percentage change in long-term potentiation 15–20 min after the tetanus was $156.9 \pm 5.0\%$ ($n = 21$) in the slope of EPSP and $181.3 \pm 7.3\%$ ($n = 21$) in the amplitude of population spike. Long-term potentiation 50–60 min after tetanus, compared with the control level, was $149.8 \pm 6.4\%$ in the slope of EPSP ($n = 21$) and $177.8 \pm 6.9\%$ in the amplitude of population spike ($n = 21$).

In untreated slices, long-term potentiation was reversed close to the pre-tetanic control level by an low-frequency stimulation of 1000 pulses at 1 Hz delivered 20 min after the tetanus (depotentiation of long-term potentiation); Fig. 2C shows a typical example. The responses immediately after low-frequency stimulation recovered slowly towards the control level, reaching a plateau level usually within a few minutes, or at most 45 min. The percentage reduction in long-term potentiation 50–60 min after low-frequency stimulation in the slope of EPSP and the amplitude of population spike were $68.5 \pm 14.4\%$ and $80.1 \pm 8.8\%$, ($n = 6$), respectively, and the percentage change in long-term potentiation were $77.2 \pm 4.8\%$ and $65.0 \pm 5.7\%$, respectively ($n = 6$, Fig. 3, DP).

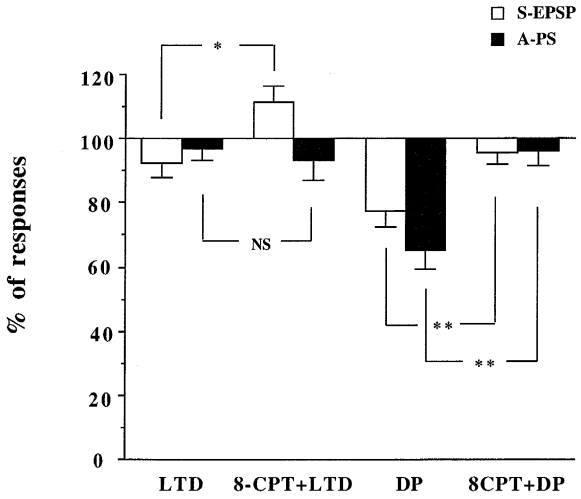

Fig. 3. Averaged percentage change in responses (open columns: the slope of EPSP, closed columns: the amplitude of population spike) recorded 50–60 min after the low-frequency stimulation (long-term depression, DP) in the absence or presence of 8-CPT (1 μM, 8-CPT+). For the long-term depression, low-frequency stimulation (1 Hz, 1,000 pulses) was applied to non-conditioned slices and the pre-low-frequency stimulation level was taken as 100%. For depotentiation of long-term potentiation (DP), low-frequency stimulation was applied 20 min after tetanus and the level of long-term potentiation was taken as 100%. ** and * indicate significant difference ($P < 0.01$ or 0.05, respectively), while NS indicates no significant difference.

When 8-CPT was applied during low-frequency stimulation, depotentiation of long-term potentiation was attenuated; a typical example is shown in Fig. 2D. Both the slope of EPSP and the amplitude of population spike after low-frequency stimulation were maintained close to the level of the previously induced long-term potentiation. The percentage reduction in long-term potentiation 50–60 min after low-frequency stimulation was $13.4 \pm 9.7\%$ for the slope of EPSP and $9.0 \pm 10.9\%$ for the amplitude of population spike ($n = 7$) and the percentage change in long-term potentiation 50–60 min after low-frequency stimulation was $95.5 \pm 3.6\%$ for the slope of EPSP and was $96.1 \pm 4.9\%$ for the amplitude of population spike ($n = 7$, Fig. 3, 8-CPT + DP).

4. Discussion

In the presence of 1 μM 8-CPT, depotentiation of long-term potentiation both as regards the slope of EPSP

and in the amplitude of population spike was blocked in terms of both the percentage reduction of long-term potentiation and the percentage change in long-term potentiation ($P < 0.01$, Fig. 3, DP and 8-CPT + DP). However, to draw this conclusion, the increased response in amplitude induced by 8-CPT by itself must be taken into consideration.

As is shown in Fig. 1C and D, following the perfusion with 8-CPT, responses were increased, the maximum effect being seen after the end of the perfusion; this was then followed by a gradual decline to the control level in the standard medium. 50 to 60 min after the end of 8-CPT perfusion, the response had almost returned to control levels, although the slope of EPSP was still significantly greater than in the control ($P < 0.05$). For this reason, responses recorded 50–60 min after the end of 8-CPT perfusion were analyzed.

If the effect of 8-CPT remained and is included in the level of response 50–60 min after low-frequency stimulation delivered in the presence of 8-CPT, the percentage reduction in long-term potentiation will be underestimated. Taking this into consideration (11.6% and 5.7% increase in the slope of EPSP and amplitude of population spike, respectively, as shown in Fig. 1D), the percentage reduction in long-term potentiation can be re-calculated as 35.7 $\pm$ 4.3% for the slope of EPSP and 28.7 $\pm$ 7.6% for the amplitude of population spike, respectively ($n = 7$), still significantly smaller ($P < 0.05$ and $P < 0.01$, respectively) than the values of the mean reduction of 68.5% and 80.1% seen for the slope of EPSP and amplitude of population spike in the control situation. These results indicate that the activation of adenosine A_1 receptors enhances depotentiation of long-term potentiation.

The increased responses due to 8-CPT raises a further problem, namely that, owing to the increased response in the presence of 8-CPT, low-frequency stimulation was started at different levels of responses in the control and test slices (Fig. 2B and D). Since the magnitude of synaptic plasticity, such as long-term potentiation, is dependent on the strength of the input stimulation, the results induced by low-frequency stimulation in the presence of 8-CPT might be due to the increased responses itself. The response to low-frequency stimulation in the presence of 8-CPT during, and immediately after, low-frequency stimulation also differs from that of low-frequency stimulation in the absence of 8-CPT, with the decline in response to low-frequency stimulation being slower and the depression just after the end of low-frequency stimulation smaller than in the control (Fig. 2), which again might be explained by the higher initial level of the responses, rather than a direct effect of 8-CPT. However, since low-frequency stimulation itself induced a rapid increase in response within 1–2 min (Fig. 2A), and since the same response pattern (slow decline and small depression of responses) was always observed when the level of responses had been increased by tetanus (Fig. 2D), it is justifiable to assume that differences in response pattern were not induced by the different starting level, but by 8-CPT itself and that 8-CPT reverses the slope of EPSP from depression (long-term depression) to potentiation, but has no effect on the amplitude of population spike (Fig. 3, long-term depression and 8-CPT + LTD). We therefore conclude that endogeneous adenosine, acting via activation of A_1 receptors, facilitates long-term depression in the EPSP, without affecting the population spike.

The effects of 8-CPT on depotentiation of long-term potentiation were quite different from those on long-term depression; both the slope of EPSP and the amplitude of population spike were decreased, but without any reversal of the slope of EPSP (Fig. 3, DP and 8-CPT + DP). Since the only procedural difference between the long-term depression and depotentiation was the absence or presence of the tetanic stimulation and since differences in response were significant, both in terms of the percentage reduction and the percentage change in response, for the depotentiation, we conclude that 8-CPT has a different effect on the long-term depression and depotentiation of long-term potentiation. This indicates that, although low-frequency stimulation was used to induce both synaptic changes, depotentiation of long-term potentiation is different, at least in pharmacological properties, from long-term depression.

The role of endogenous adenosine A_1 receptors can be discussed from the point of modulatory functions of synaptic plasticity. Activation of adenosine A_1 receptors inhibits long-term potentiation development (Arai et al., 1990), but, as reported in this paper, facilitates depotentiation of long-term potentiation. These modulatory effects contrast markedly with the effect of activation A_2 receptors, which results in the facilitation of long-term potentiation and inhibition of depotentiation of long-term potentiation.

To evaluate the functional role of adenosine A_1 receptors, following three facts can be taken into consideration: (1) The release of ATP and adenosine derivatives from the presynaptic terminals into the synaptic cleft is dependent on stimulus frequency (Schubert et al., 1976, 1979; White, 1978; Wieraszko et al., 1989), (2) the affinity of adenosine for A_1 receptors is higher (nanomolar range) than that for adenosine A_2 receptors (micromolar range) (Bruns et al., 1980; Londos et al., 1980) and (3) the activation of A_2 receptors in hippocampal CA1 neurons reduces the activity of A_1 receptors via a cross-talk between A_2 and A_1 receptors (Cunha et al., 1994).

It is also possible that, due to the degree of release, up-take and diffusion, the concentration of adenosine and its derivatives is higher in regions in which synapses are activated than in the surrounding region. This center-surround concentration gradient corresponds to the activation map of the receptor types, with A_1 and A_2 receptors being activated in the central region and A_1 in the surrounding region. In the central region, however, A_2 receptors may predominantly be activated because of cross-talk and may

facilitate long-term potentiation formation and inhibit depotentiation of long-term potentiation in terms of the slope of EPSP (Sekino et al., 1991; Fujii et al., 1992). In contrast, in the surrounding region, activation of A_1 receptors by endogenous adenosine and its derivatives will inhibit long-term potentiation (Arai et al., 1990) and, as is shown in this study, facilitate the depotentiation of long-term potentiation. Thus, it is possible that one of the roles of the high-affinity A_1 receptors is the sculpturing of synaptic plasticity by means of this chemical center-surround organization (Kuroda, 1991). To determine the cellular mechanism of the modulatory function after the activation of A_1 receptors, further study will be needed.

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