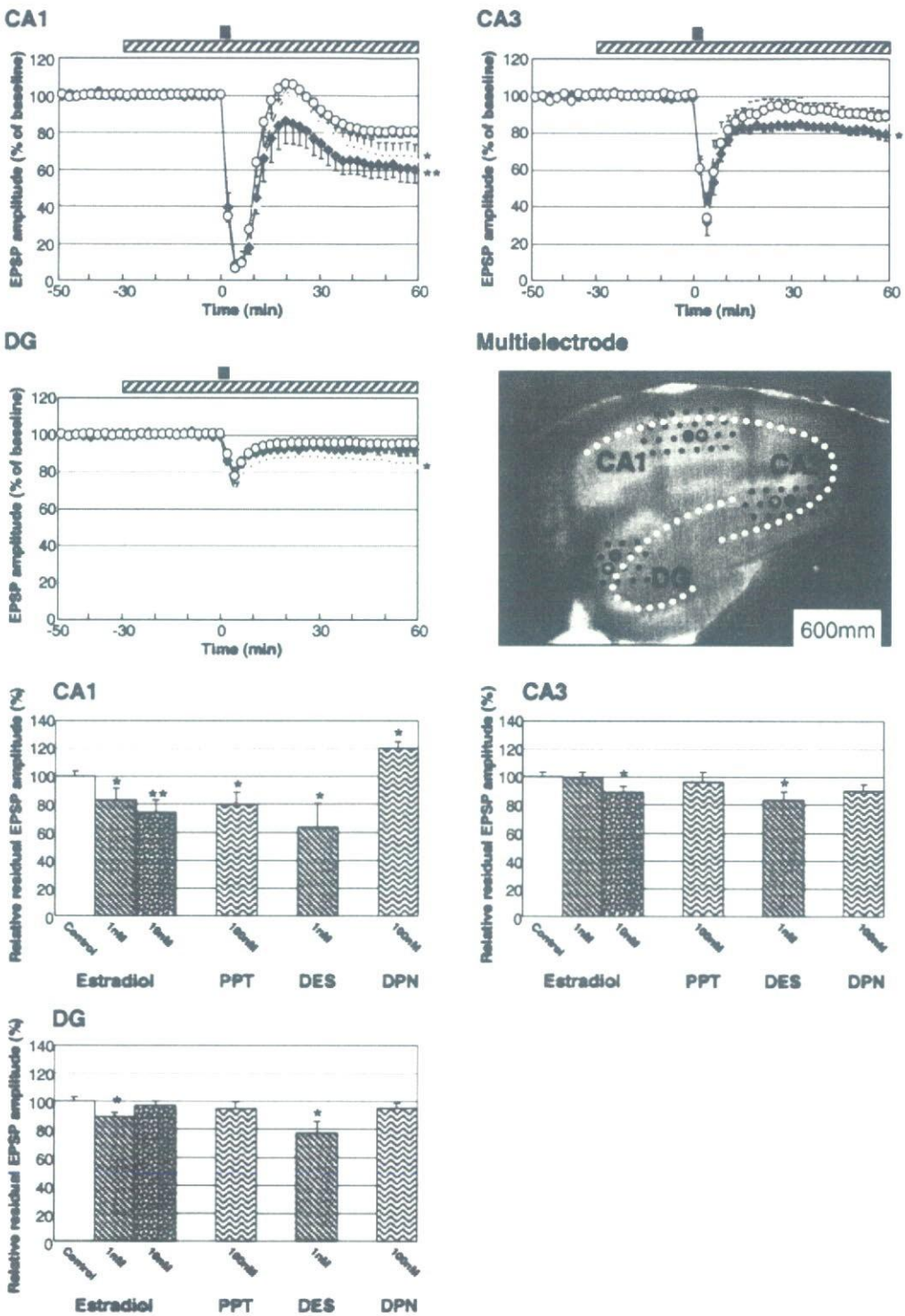
spines that creates sites for new neuronal contacts. We demonstrated that dendritic spines were rapidly modulated by estradiol application, using single spine analysis of Lucifer-Yellow-injected neurons in adult male hippocampal slices (Komatsuzaki et al., 2005; Tsurugizawa et al., 2005). Following a 2 h treatment with estradiol in the stratum radiatum of CA1 region, the treated dendrites have significantly more spines at 1 nM estradiol (1.31 spines/μm) than dendrites at 0 nM estradiol (0.85 spines/μm) (Fig. 3A) (Mukai et al., 2007). PPT induced a significant enhancement of the spine density to 1.20 spines/μm. However, DPN increased the spine density only slightly (0.95 spines/μm). Blocking of ERα by ICI 182,780 completely suppressed the enhancing effect of estradiol on the spine density. Blocking of phosphorylation of Erk MAP kinase by



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PD98059 completely prevented the estradiol-induced spinogenesis. Taken together, the enhancement of the spine density is probably induced by activation of Erk MAP kinase by estradiol-bound ERα at the basal low Ca^{2+} concentration of around 0.1–0.2 μM in resting neurons (Ishii et al., 2006). When the Ca^{2+} concentration in spines was further decreased by blocking NMDA receptors with MK-801, the enhancing effect by estradiol was completely suppressed. Function of estradiol-bound ERα therefore needs the basal level of Ca^{2+} concentration of around 0.1–0.2 μM. The morphological changes in CA1 spines occurred by 2 h estradiol treatments. In control slices (0 nM estradiol), the relative population of spines was approximately 24% for mushroom spine, 62% for thin spine, 1% for filopodium and 13% for stubby spine. Upon 1 nM estradiol treatment, the density of thin spine was selectively increased, from 0.57 spines/μm to 0.97 spines/μm, while the density of mushroom and stubby was not significantly altered (Fig. 3A).

The spine density is not always increased but in some cases decreased by the estradiol treatment. The estradiol-induced spinogenesis is highly region specific and heterogeneous. In fact, in CA3 pyramidal neurons, the total density of thorns of thorny excrescencies (spine-like postsynaptic structures in the stratum lucidum of CA3, having contacts with mossy fiber terminals originated from granule cells) decreased dramatically to approximately 70% upon a 2 h treatment of 1 nM estradiol (Fig. 3B) (Tsurugizawa et al., 2005). PPT significantly decreased the density of thorns from 2.19 to 1.66 thorns/μm, but DPN did not significantly change the density of thorns (Fig. 3B). Blocking of Erk MAP kinase by PD98059 completely prevented the estradiol-induced decrease of thorns. Taken together, in the stratum lucidum of CA3, the decrease of the thorn density is probably induced by activation of Erk MAP kinase by estradiol-bound ERα at the basal Ca^{2+} concentration of around 0.1–0.2 μM. When the Ca^{2+} concentration was decreased to below the basal level by blocking AMPA receptors with CNQX, or by changing the outer medium to Ca^{2+}-free ACSF, the suppression effect of estradiol was completely inhibited (Fig. 3B). These results suggest that the decrease of thorns requires the basal Ca^{2+} concentration which is kept by spontaneous postsynaptic Ca^{2+} influx via voltage activated calcium channels depending upon AMPA receptor-mediated spontaneous voltage fluctuations, because the spontaneous Ca^{2+} influx within thorny excrescencies occurs mainly via voltage activated calcium channels (Baude et al., 1995; Fritschy et al., 1998; Monaghan et al., 1983; Reid et al., 2001; Reid, 2002). Note that blocking of NMDA receptors by MK-801 did not prevent the estradiol-induced decrease of thorns. This may be due to much smaller contribution of NMDA receptors to the spontaneous Ca^{2+} influx within thorns than that of voltage activated calcium channels. The function of estradiol-bound ERα therefore needs the basal level of Ca^{2+} concentration around 0.1–0.2 μM.

We always use acute hippocampal slices in order to examine the direct effect of estradiol on glutamatergic neurons within slices. Results from *in vivo* investigations using whole rat may reflect not only direct but also indirect effects of estradiol on glutamatergic neurons via cholinergic or serotonergic neurons, projecting to the hippocampus (MacLusky et al., 2005).

The rapid effect of estrogens has also been observed *in vivo*. Leranth, MacLusky and co-workers have demonstrated that the estradiol (60 μg/kg) increases the spine-synapse density due to synaptic rearrangements in ovariectomized adult rats as rapid as after 30 min of estradiol injection using electron micrographic analysis (MacLusky et al., 2005). On the other hand, over decades, the slow genomic effects (1–4 days) of estradiol on spine plasticity have been extensively investigated *in vivo*. For example, supplement of estrogens in ovariectomized adult female rats (Gould et al., 1990; MacLusky et al., 2005; Woolley et al., 1990; Woolley and McEwen, 1992) increases the density of spines in the stratum radiatum of CA1 pyramidal neurons, resulting in recovery of spines to the level of wild rat. These effects of enhancement in spinogenesis have also been observed as rapid as at 4.5 h after s.c. injection of estrogen (MacLusky et al., 2005). *In vitro* investigations have also shown that spine density in CA1 increases following several days' treatment of cultured hippocampal slices with exogenous estradiol (Pozzo-Miller et al., 1999). The contribution of endogenous estradiol has been reported by Rune and co-workers who demonstrated that the suppression of endogenous estradiol synthesis by letrozole treatments for 4 days significantly decreased the spine density in the stratum radiatum of the CA1 region in cultured slices (Kretz et al., 2004).

2.3. *Synaptic membrane receptors*

What is the receptor of 17β-estradiol that mediates rapid actions (0.5–2 h) on synaptic plasticity in the hippocampus? Putative synaptic membrane estrogen receptors remain poorly defined. Many attempts have been made to identify

Fig. 2 – Rapid modulation of LTD by 17β-estradiol in hippocampal slices from adult male rats. (Upper CA1, CA3 and DG) Time dependence of maximal EPSP amplitude in CA1 (CA1), CA3 (CA3) and DG (DG). Estradiol concentration was 0 nM (open circle), 1 nM (yellow closed triangle) and 10 nM (red closed diamond), respectively. (Multielectrode) Custom-made 64 multielectrode probe (MED64, Panasonic, Japan) with the hippocampal slice. Stimulation (red circle) and recording (blue circle) electrodes are indicated. Here, 100% EPSP amplitude refers to the EPSP value at $t=-40$ min prior to NMDA stimulation, irrespective of the test condition. LTD was induced by 30 μM NMDA perfusion at time $t=0$ to 3 min (closed bar above the graph). Hatched bar above the graph indicates period of time during which estradiol was administered. The LTD enhancement was reproducibly observed in more than 90 slices out of 100 slices. (Lower CA1, CA3 and DG) Comparison of modulation effect of LTD by 17β-estradiol and agonists in the CA1 (CA1), CA3 (CA3) and DG (DG) of hippocampal slices. Vertical axis is relative EPSP amplitude at $t=60$ min, where EPSP amplitude at $t=60$ min of the control slice without drug application is taken as 100%. From left to right, 17β-estradiol (Estradiol), PPT, DES and DPN at indicated concentrations. Note that coperfusion of 1 μM ICI with 10 nM 17β-estradiol did not suppress the enhancing effect of LTD by estradiol (data not shown). The significance of the estradiol effect was confirmed at 60 min via statistical analysis using ANOVAs (*$p<0.05$; **$p<0.01$). [Modified from Mukai et al. (2007)].

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membrane estrogen receptors. At the present stage, the most probable candidates for membrane estrogen receptors may be ERα, ERβ and GPR30.

Why are classical nuclear type receptors ERα and ERβ candidates? Because ICI do not suppress estradiol-induced rapid modulation of electrophysiological properties such as LTD, LTP and kinate-induced currents, classical estrogen receptors are suggested to be not involved in these modulations (Gu and Moss, 1996). However, these results do not eliminate the possibility that ERα and ERβ could drive these synaptic transmissions. ICI has been indicated to display its effect by inhibiting dimerization of ERα and ERβ. If dimerization processes are not involved in rapid modulation of electrophysiological phenomena, then ICI cannot block these phenomena. On the other hand, rapid enhancement of spinogenesis via ERα was significantly blocked by ICI (Fig. 3B) (Mukai et al., 2007), therefore dimerization processes occur for synaptic ERα in spinogenesis.

After several years of careful investigations, we successfully identified the membrane estrogen receptor ERα localized in the spines of hippocampal pyramidal and granule neurons by means of immunoelectron microscopic analysis as well as Western blot analysis using affinity-column purified anti-ERα antibody RC-19 (Mukai et al., 2007). A postembedding immunogold electron microscopic analysis demonstrated the synaptic localization of ERα in the glutamatergic neurons in CA1, CA3 and DG (Fig. 4). ERα was also localized in the nuclei. Western blot analysis demonstrated that ERα (67 kDa) and Erk MAP kinase were tightly associated with postsynaptic density fractions (PSD). Because the estradiol-induced modulation of LTD and spine density appeared so rapidly in the time range of 1–2 h, the synaptic ERα observed at PSD and postsynaptic compartments probably plays an essential role in driving rapid processes. It should be noted that specific binding of purified RC-19 antibody to real ERα (67 kDa) in the hippocampus was verified using MALDI-TOF mass-spectrometric analysis of RC-19 reacted proteins as well as the absence of reactivity of RC-19 with ERαKO mice hippocampus (Fig. 5) (Mukai et al., 2007). These analyses are essential in the hippocampus, because we found that non-purified MC-20 antisera, frequently used in previous investigations, often reacted with 62 kDa unknown proteins in the brain and did not significantly react with real ERα (67 kDa) (Mukai et al., 2007). AS409, another frequently used antisera, did mainly react with unknown proteins different from real ERα (Mukai et al., 2007). Non-purified antisera may largely react with proteins having amino acid sequences similar to the real antigen in the hippocampus in which extremely low level of ERα is expressed as compared with that in the ovary (Fig. 6). ERα antisera are normally examined for their reactivity only in endocrine organs such as the ovary in which ERα is highly expressed. Therefore, staining patterns with non-purified antisera probably do not show real ERα distribution in the hippocampus. Antisera should be purified before application to the hippocampus.

ERβ has been reported to associate with membranes in genetically expressed CHO cells and MCF-7 cells (Pedram et al., 2006; Razandi et al., 1999). Several investigations of immunostaining of ERβ have suggested extranuclear expression of ERβ including dendritic appearance in the hippocampal principal neurons (Milner et al., 2005). ERβ is, however, not yet identified as synaptic membrane receptors. Subcellular immuostaining patterns of these reports might reflect relatively

Fig. 3 – Changes in the density and morphology of spines in CA1 (A1-A3) or thorns in CA3 (B1-B3) upon treatments of 17β-estradiol (E2) and drugs in hippocampal slices from adult male rats. Spines/thorns were analyzed along the dendrites of pyramidal neurons. (A1) Confocal micrographs showing spines along the secondary dendrites of hippocampal CA1 pyramidal neurons. (Left) A whole image of Lucifer Yellow-injected CA1 neuron. Vertical bar, 100 μm. (Right) Maximal intensity projections onto *XY* plane from *z*-series confocal micrographs, showing spines along the dendrites. From middle to bottom, spines along the apical dendrite in stratum radiatum (Control and E2), and spines along the apical dendrite in stratum lacunosum-moleculare (Control and E2); horizontal bar, 2 μm. Slices were treated in artificial cerebrospinal fluid (ACSF) for 2 h without drugs (Control) or with 1 nM E2 (E2). ACSF contains 2 mM Ca^{2+} and 2 mM Mg^{2+}. (A2) Effect of drug treatments on the total spine density of CA1 neurons in the stratum radiatum (s.r.). Vertical axis is the average number of spines per 1 μm of dendrite. A 2 h treatment in ACSF without drugs (Control), with 1 nM E2 (E2), with 100 nM PPT (PPT), with 100 nM DPN (DPN), with 1 nM E2 and 1 μM ICI 182,780 (ICI+E2), with 1 nM E2 and 20 μM CNQX (CNQX+E2), with 1 nM E2 and 50 μM MK-801 (MK+E2), with 1 nM E2 and 50 μM PD98059 (PD+E2). (A3) Density of 4 subtypes of spines in the CA1 stratum radiatum. A 2 h treatment in ACSF without drugs (Control group), with 1 nM E2 (E2 group), with 100 nM PPT (PPT group), with 1 nM E2 and 1 μM ICI (ICI+E2 group), with 1 nM E2 and 50 μM MK-801 (MK+E2 group), with 1 nM E2 and 50 μM PD98059 (PD+E2 group). In each group, from left to right, mushroom (black column), thin (dotted column), filopodium (hatched column) and stubby (open column). (B1) Maximal intensity projections onto *XY* plane from *z*-series confocal micrographs, showing thorns along the primary/secondary dendrites and spines along the secondary dendrites of hippocampal CA3 pyramidal neurons. (Upper middle) Thorny excrescencies along the primary dendrite in stratum lucidum, scale bar 2 μm. (Upper right) Spines along the apical dendrite in stratum radiatum, scale bar 2 μm. Thorny excrescencies have bulbous-shaped huge heads named thorns (red circles) which are different from spines with separated distribution (yellow circles). (Lower image) A whole image of Lucifer Yellow-injected CA3 neuron. Horizontal bar, 100 μm. (B2) Maximal intensity projections onto *XY* plane from *z*-series confocal micrographs, showing thorns in the CA3 stratum lucidum without drug treatments (control) and thorns after estradiol treatments (E2). Scale bar, 5 μm. (B3) Effect of drug treatments on the average number of thorns per 1 μm dendritic segment in CA3. A 2 h treatment in ACSF without estradiol (control), with 1 nM estradiol (E2), with 100 nM PPT (PPT), with 100 nM DPN (DPN), with 1 nM estradiol and 20 μM CNQX (E2+CNQX), with 1 nM estradiol and 50 μM MK-801 (E2+MK), with 1nM estradiol in ACSF not containing Ca^{2+} (E2 without Ca^{2+}) and with 1 nM estradiol and 20 μM PD98059 (E2+PD). Statistical significance ($^{*}p<0.05$; $^{**}p<0.01$). [Modified from Mukai et al. (2007), Murakami et al. (2006) and Tsurugizawa et al. (2005)].

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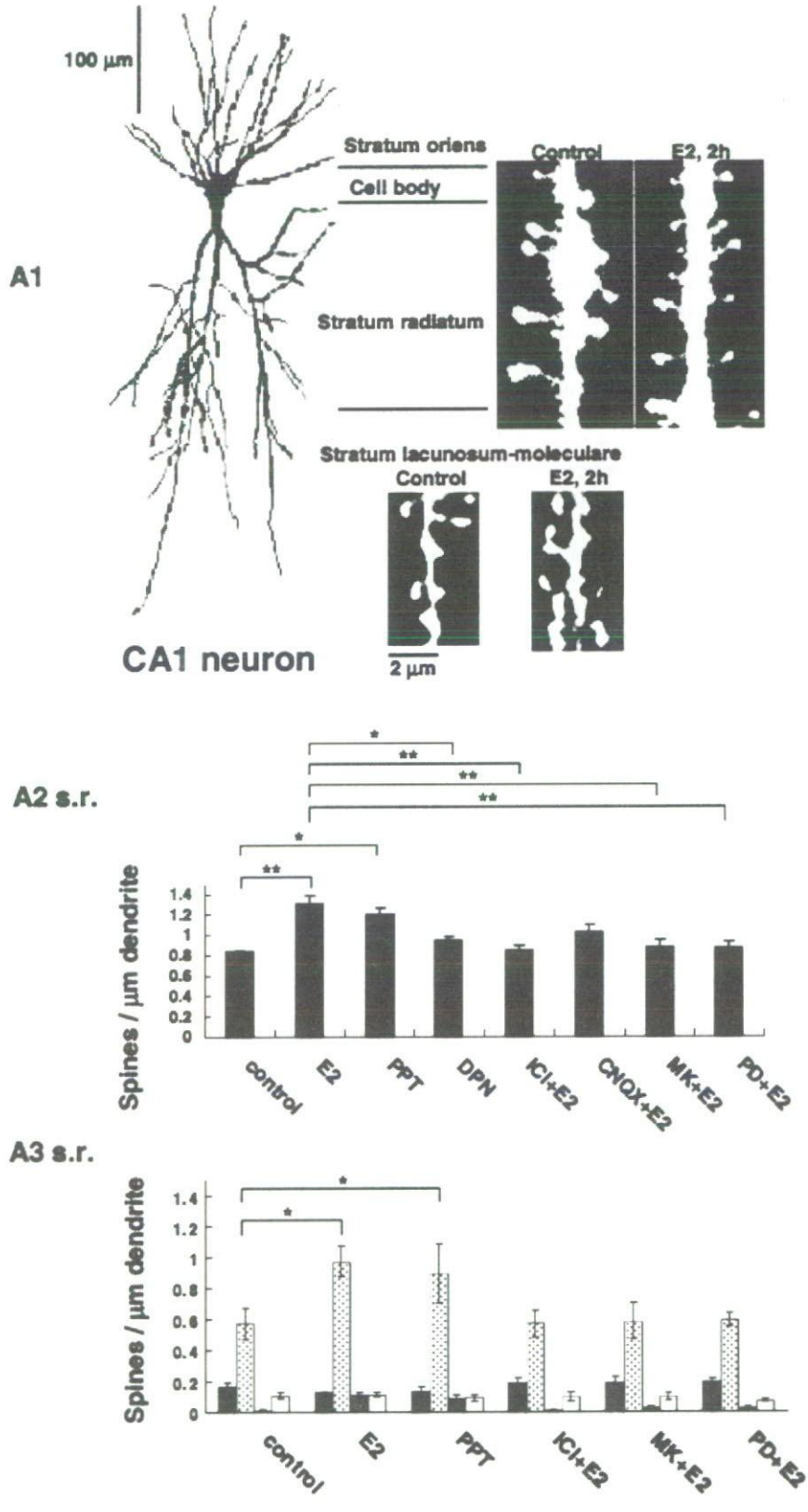
minor expression of ERβ and major expression of unknown proteins, due to multiple reactivity of non-purified ERβ antisera to several unknown proteins in Western blot analysis of hippocampal tissues. The purity of commercially available ERβ antisera may be worse than that of ERα antisera as judged from Western blot analysis.



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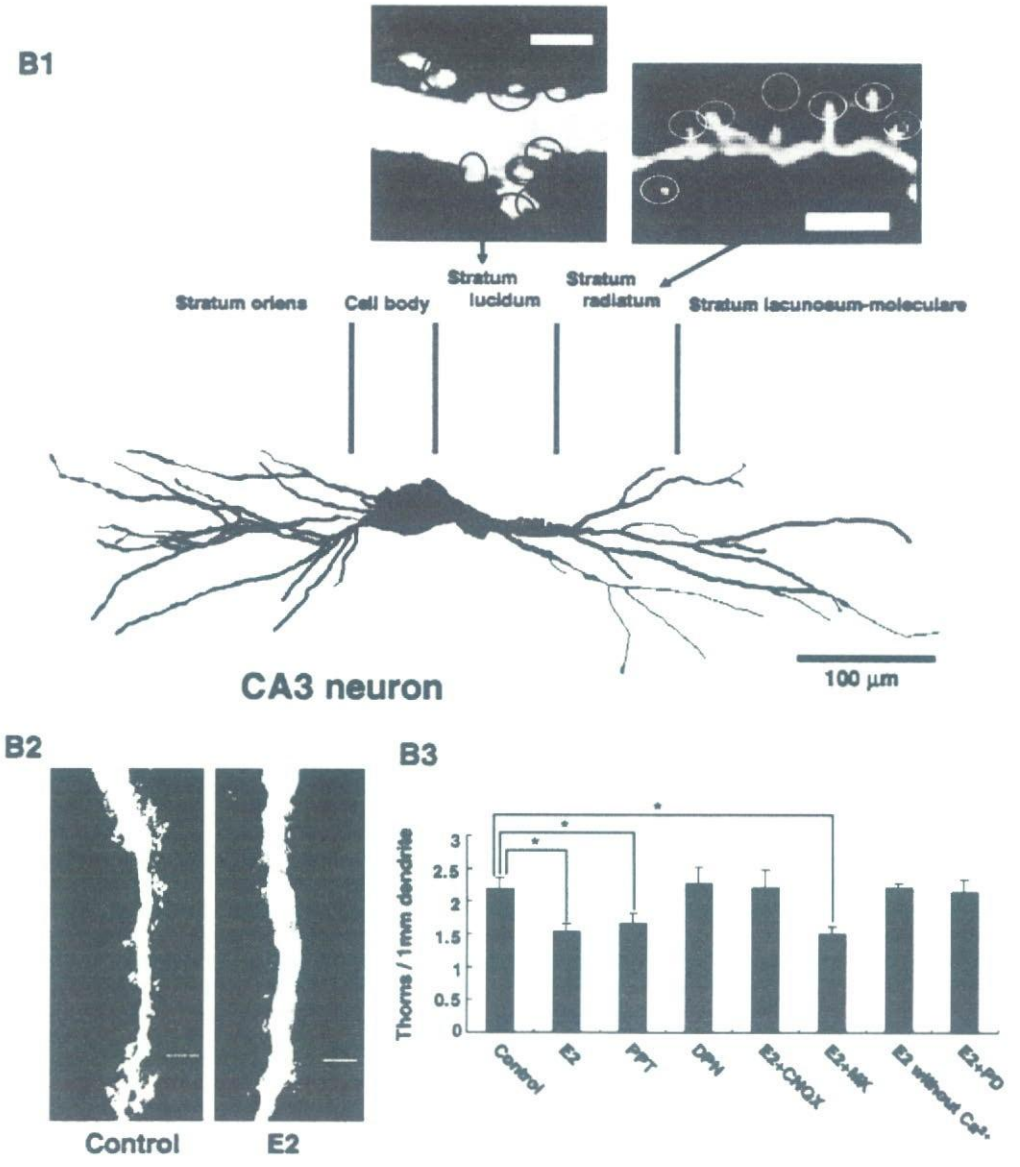

Fig. 3 (*continued*).

Recently, transmembrane G-protein coupled estrogen receptor GPR30 has been identified in the plasma membrane of SKBR3 breast cancer cells that lack ERα and ERβ (Thomas et al., 2005) as well as in endoplasmic reticulum membranes of COS7 after genetic expression of GPR30 fused with Green Fluorescent Protein (Revankar et al., 2005). Because expression of GPR30 has also been observed in the hippocampal neurons (Brailoiu et al., 2007), further investigations may reveal its contribution to rapid estradiol modulation of synaptic plasticity.

3. Action of endocrine disrupters on synaptic plasticity

We investigated rapid modulation by endocrine disrupters (low dose of environmental chemicals) of synaptic plasticity in the adult male rat (3 months) hippocampus, by comparison with the estradiol effects (Kawato, 2004). Typical endocrine disrupters were used such as BPA (synthetic material of polycarbonate resin used in dental prostheses, sealants and baby bottles), DES (a synthetic estrogen for preventing miscarriages), nonylphenol and octylphenol (NP and OP, used as surfactants, plasticizers and supplement of resins).

The effect of low dose BPA, DES, NP and OP was clearly detectable with the NMDA-induced LTD analysis in CA1, CA3 and DG of the same slices using multielectrode probes (Ogiue-Ikeda et al., 2005; Kawato et al., 2007). A 30 min perfusion of both 10–100 nM BPA and 1 nM DES significantly enhanced LTD in both CA1 and CA3. The percentage of LTD enhancement was 10–20% for BPA and approximately 35% for DES. On the other hand, both 100 nM NP and 100 nM OP suppressed LTD by approximately 10% in CA1 but enhanced by approximately 10% in CA3. In DG, BPA suppressed LTD; however, DES and NP enhanced LTD, while OP did not induce any significant change in LTD. Taken

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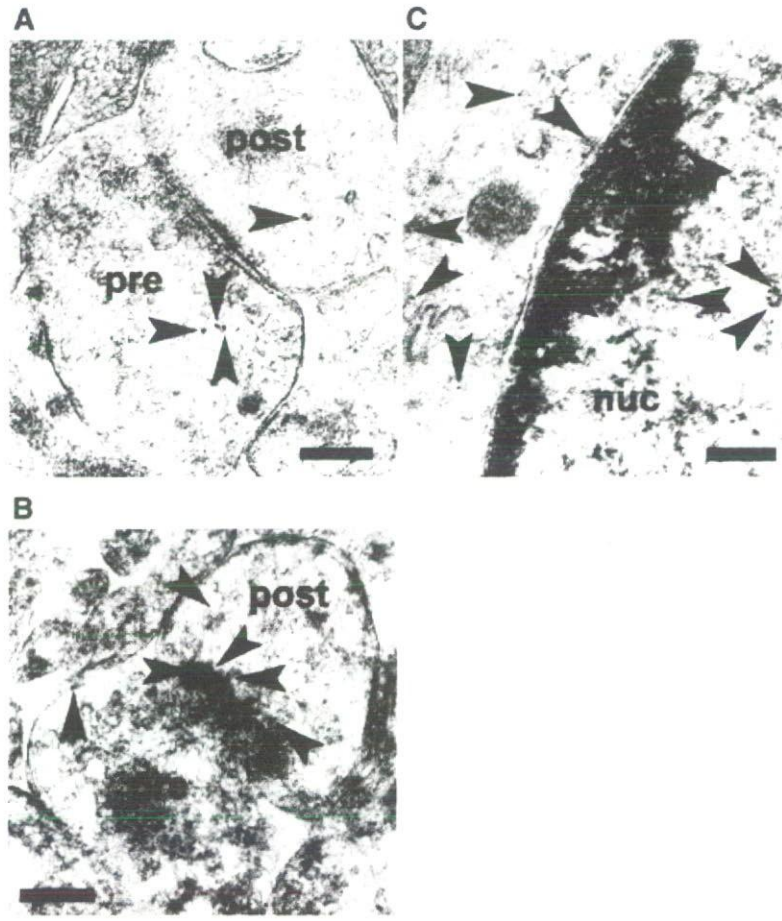

Fig. 4 – Immunoelectron microscopic analysis of the distribution of ERα within axospinous synapses, in the stratum radiatum of the hippocampal slices from adult male rat. (A) Gold particles (arrowheads) were localized in the pre- and postsynaptic regions. (B) In dendritic spines, gold particles were associated with PSD regions. (C) Gold particles were also localized in the nuclei. Pre, presynaptic region; Post, postsynaptic region; Scale bar, 200 nm. [Modified from Mukai et al. (2007)].

collectively, the effect of endocrine disrupters on LTD was classified into two types, BPA/DES type and NP/OP type. BPA and DES induced the LTD enhancement in CA1 and CA3, which is a similar effect to that of estradiol. NP and OP induced the LTD suppression in CA1 as well as the LTD enhancement in CA3, which is a different effect from that of estradiol.

The effect of endocrine disrupters was also observed on spinogenesis (Tanabe et al., 2005). The density and morphology of dendritic spines were analyzed by imaging Lucifer Yellow-injected CA1 neurons in hippocampal slices. The total spine density was significantly increased by 10 nM BPA and 1 nM DES in the hippocampal CA1. In particular, the thin spine was selectively increased by BPA and DES. These BPA effects are similar to estradiol effects. As additional investigations, a low dose BPA at 10–100 nM transiently increased the intracellular Ca^{2+} level of hippocampal neurons via activation of non-genomic pathway within 20 s (Tanabe et al., 2006).

Is membrane-associated ERα or ERβ a possible receptor for endocrine disrupters? BPA might activate ERα as judged from our results of LTD and spinogenesis. However, the binding affinity of BPA to water soluble ERα has been reported to be much lower (approximately 1/2000) than that of 17β-estradiol (Kuiper et al., 1997). The ligand binding affinity of BPA to ERα has been shown to be 1/100–1/1000 of that of 17β-estradiol (Morohoshi et al., 2005). These reports, however, might not conflict to the reported low dose effect of BPA at nanomolar level, if we take into account the significant concentration processes of BPA in the membrane where membrane bound estrogen receptors exist.

The rapid effect of BPA has also been observed *in vivo*. Leranth, MacLusky and co-workers demonstrated that the estradiol-induced increase in the spine-synapse density was inhibited by the simultaneous application of BPA (40 μg/kg body weight) and estradiol (60 μg/kg) in ovariectomized rats for 30 min (MacLusky et al., 2005). It has been also demonstrated that a moderate dosage of 300 μg/kg BPA alone suppressed the spine-synapse density in the CA1 region of the hippocampus in ovariectomized rats (MacLusky et al., 2005). It should be noted that results from *in vivo* investigations may reflect not only direct effects within the hippocampus but also indirect effects of estradiol via cholinergic or serotonergic neurons, projecting to the hippocampus (MacLusky et al., 2005).

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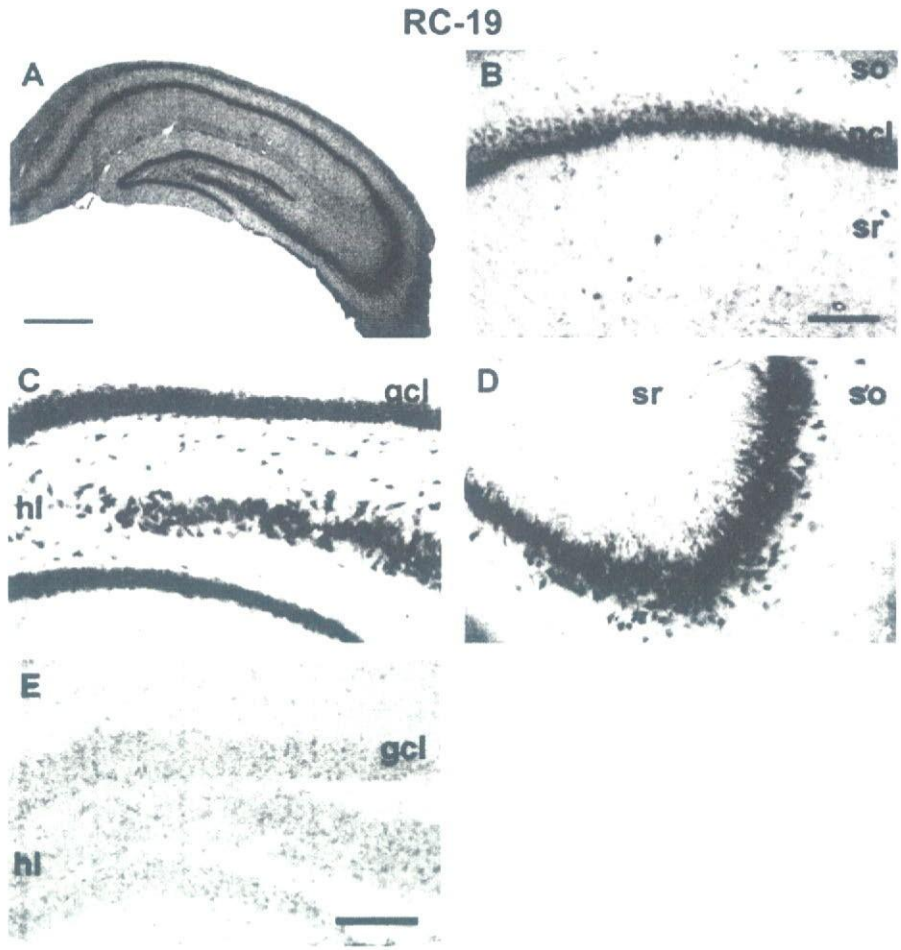

Fig. 5 – Immunohistochemical staining of ERα with RC-19 antibody in the hippocampal slices from adult male rat (A–D) and adult ERαKO mouse (E). (A) Coronal section of the whole hippocampal formation; (B) CA1; (C) DG; (D) CA3; (E) DG of ERαKO mouse. so, stratum oriens; pcl, pyramidal cell layer; sr, stratum radiatum; gcl, granule cell layer; hl, hilus. Scale bar, 500 μm for A, and 200 μm for B–E. [Modified from Mukai et al. (2007)].

Chronic effects of environmental chemicals on reproductive organs have been intensively investigated, primarily toxic effects of high dose environmental chemicals have been investigated about the development and functions of the reproduction systems (Al-Hiyasat et al., 2002; Fisher et al., 1999; Grote et al., 2004; Halldin et al., 2005). For example, treatment

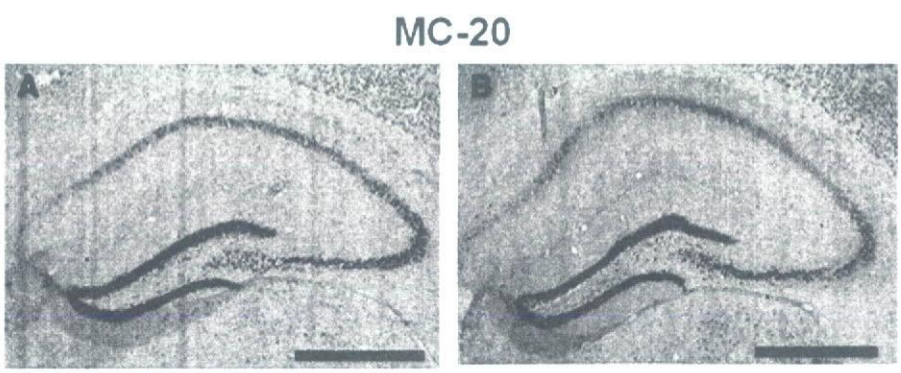

Fig. 6 – Immunohistochemical staining with MC-20 antiserum in the hippocampal slices from adult ERαKO (A) and wild male mice (B). (A and B) The coronal section of the whole hippocampal formation. Scale bar, 50 μm. [Modified from Mukai et al. (2007)].

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with BPA (37 mg/kg body weight/day for 18–25 days), DES (0.37 or 0.037 mg/kg/day for 18–25 days) and OP (150 mg/kg/day for 18–25 days) in neonatal stage has been reported to cause a decrease in epithelial cell height of the efferent ducts in the testis of young male rats (Fisher et al., 1999). Note that mg/kg high dosage may induce micromolar plasma concentration of environmental chemicals.

Human BPA exposure (at μg/kg low dosage) is concluded to be insufficient to elicit significant estrogenic responses in endocrine organs and gonads due to the low affinity of BPA for the cell nuclear estrogen receptors, ERα and ERβ, as well as weak bioactivity in standard tests of estrogenicity, such as the rat uterotrophic assay (Ashby, 2001; Degen et al., 2002; EC Scientific Committee on Food, 2002; Japan Ministry of the Environment's ExTEND 2005; U.S. Environmental Protection Agency (EPA) 1993). However, because μg/kg low dosage may induce nanomolar plasma concentration of endocrine disrupters, we emphasize that our investigations about the hippocampus imply that even nanomolar low dosage of endocrine disrupters could induce significant effects on memory processes.

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