Supplemental Reference

Adams MM, Fink SE, Shah RA, Janssen WG, Hayashi S, Milner TA, McEwen BS, Morrison JH (2002) Estrogen and aging affect the subcellular distribution of estrogen receptor-alpha in the hippocampus of female rats. J Neurosci 22:3608-3614.

Bi R, Broutman G, Foy MR, Thompson RF, Baudry M (2000) The tyrosine kinase and mitogen-activated protein kinase pathways mediate multiple effects of estrogen in hippocampus. Proc Natl Acad Sci U S A 97:3602-3607.

Bi R, Foy MR, Vouimba RM, Thompson RF, Baudry M (2001) Cyclic changes in estradiol regulate synaptic plasticity through the MAP kinase pathway. Proc Natl Acad Sci U S A 98:13391-13395.

Cardona-Gomez GP, DonCarlos L, Garcia-Segura LM (2000) Insulin-like growth factor I receptors and estrogen receptors colocalize in female rat brain. Neuroscience 99:751-760.

Clarke CH, Norfleet AM, Clarke MS, Watson CS, Cunningham KA, Thomas ML (2000) Perimembrane localization of the estrogen receptor alpha protein in neuronal processes of cultured hippocampal neurons. Neuroendocrinology 71:34-42.

Dupont S, Krust A, Gansmuller A, Dierich A, Chambon P, Mark M (2000) Effect of single and compound knockouts of estrogen receptors alpha (ERalpha) and beta (ERbeta) on mouse reproductive phenotypes. Development 127:4277-4291.

Hart SA, Patton JD, Woolley CS (2001) Quantitative analysis of ER alpha and GAD colocalization in the hippocampus of the adult female rat. J Comp Neurol 440:144-155.

Hojo Y, Hattori TA, Enami T, Furukawa A, Suzuki K, Ishii HT, Mukai H, Morrison JH, Janssen WG, Kominami S, Harada N, Kimoto T, Kawato S (2004) Adult male rat hippocampus synthesizes estradiol from pregnenolone by cytochromes P45017{alpha} and P450 aromatase localized in neurons. Proc Natl Acad Sci U S A 101:865-870.

Ivanova T, Beyer C (2000) Ontogenetic expression and sex differences of aromatase and estrogen receptor-alpha/beta mRNA in the mouse hippocampus. Cell Tissue Res 300:231-237.

Kawato S, Hojo Y, Kimoto T (2002) Histological and metabolism analysis of P450 expression in the brain. Methods Enzymol 357:241-249.
Kimoto T, Tsurugizawa T, Ohta Y, Makino J, Tamura H, Hojo Y, Takata N, Kawato S (2001) Neurosteroid synthesis by cytochrome p450-containing systems localized in the rat brain hippocampal neurons: N-methyl-D-aspartate and calcium-dependent synthesis. Endocrinology 142:3578-3589.
Kretz O, Fester L, Wehrenberg U, Zhou L, Brauckmann S, Zhao S, Prange-Kiel J, Naumann T, Jarry H, Frotscher M, Rune GM (2004) Hippocampal synapses depend on hippocampal estrogen synthesis. J Neurosci 24:5913-5921.
Laflamme N, Nappi RE, Drolet G, Labrie C, Rivest S (1998) Expression and neuropeptidergic characterization of estrogen receptors (ERalpha and ERbeta) throughout the rat brain: anatomical evidence of distinct roles of each subtype. J Neurobiol 36:357-378.
Leranth C, Petnehazy O, MacLusky NJ (2003) Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. J Neurosci 23:1588-1592.
MacLusky NJ, Luine VN, Hajszan T, Leranth C (2005) The 17alpha and 17beta isomers of estradiol both induce rapid spine synapse formation in the CA1 hippocampal subfield of ovariectomized female rats. Endocrinology 146:287-293.
McEwen B (2002) Estrogen actions throughout the brain. Recent Prog Horm Res 57:357-384.
Milner TA, McEwen BS, Hayashi S, Li CJ, Reagan LP, Alves SE (2001) Ultrastructural evidence that hippocampal alpha estrogen receptors are located at extranuclear sites. J Comp Neurol 429:355-371.
O'Dowd BF, Nguyen T, Marchese A, Cheng R, Lynch KR, Heng HH, Kolakowski LF, Jr., George SR (1998) Discovery of three novel G-protein-coupled receptor genes. Genomics 47:310-313.
Okamura H, Yamamoto K, Hayashi S, Kuroiwa A, Muramatsu M (1992) A polyclonal antibody to the rat oestrogen receptor expressed in Escherichia coli: characterization and application to immunohistochemistry. J Endocrinol 135:333-341.
Orikasa C, McEwen BS, Hayashi H, Sakuma Y, Hayashi S (2000) Estrogen receptor alpha, but not beta, is expressed in the interneurons of the

hippocampus in prepubertal rats: an in situ hybridization study. Brain Res Dev Brain Res 120:245-254.
Pendaries C, Darblade B, Rochaix P, Krust A, Chambon P, Korach KS, Bayard F, Arnal JF (2002) The AF-1 activation-function of ERalpha may be dispensable to mediate the effect of estradiol on endothelial NO production in mice. Proc Natl Acad Sci U S A 99:2205-2210.
Powell CE, Soto AM, Sonnenschein C (2001) Identification and characterization of membrane estrogen receptor from MCF7 estrogen-target cells. J Steroid Biochem Mol Biol 77:97-108.
Pozzo-Miller LD, Inoue T, Murphy DD (1999) Estradiol increases spine density and NMDA-dependent Ca2+ transients in spines of CA1 pyramidal neurons from hippocampal slices. J Neurophysiol 81:1404-1411.
Rune GM, Wehrenberg U, Prange-Kiel J, Zhou L, Adelmann G, Frotscher M (2002) Estrogen up-regulates estrogen receptor alpha and synaptophysin in slice cultures of rat hippocampus. Neuroscience 113:167-175.
Shughrue PJ, Merchenthaler I (2000) Evidence for novel estrogen binding sites in the rat hippocampus. Neuroscience 99:605-612.
Shughrue PJ, Lane MV, Merchenthaler I (1997) Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. J Comp Neurol 388:507-525.
Solum DT, Handa RJ (2001) Localization of estrogen receptor alpha (ER alpha) in pyramidal neurons of the developing rat hippocampus. Brain Res Dev Brain Res 128:165-175.
Thomas P, Pang Y, Filardo EJ, Dong J (2005) Identity of an estrogen membrane receptor coupled to a G protein in human breast cancer cells. Endocrinology 146:624-632.
Toran-Allerand CD, Guan X, MacLusky NJ, Horvath TL, Diano S, Singh M, Connolly ES, Jr., Nethrapalli IS, Tinnikov AA (2002) ER-X: a novel, plasma membrane-associated, putative estrogen receptor that is regulated during development and after ischemic brain injury. J Neurosci 22:8391-8401.
Weiland NG, Orikasa C, Hayashi S, McEwen BS (1997) Distribution and hormone regulation of estrogen receptor immunoreactive cells in the hippocampus of male and female rats. J Comp Neurol 388:603-612.

Woolley CS, McEwen BS (1994) Estradiol regulates hippocampal dendritic spine density via an N-methyl-D-aspartate receptor-dependent mechanism. J Neurosci 14:7680-7687.

Woolley CS, Weiland NG, McEwen BS, Schwartzkroin PA (1997) Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. J Neurosci 17:1848-1859.

Fig. S1

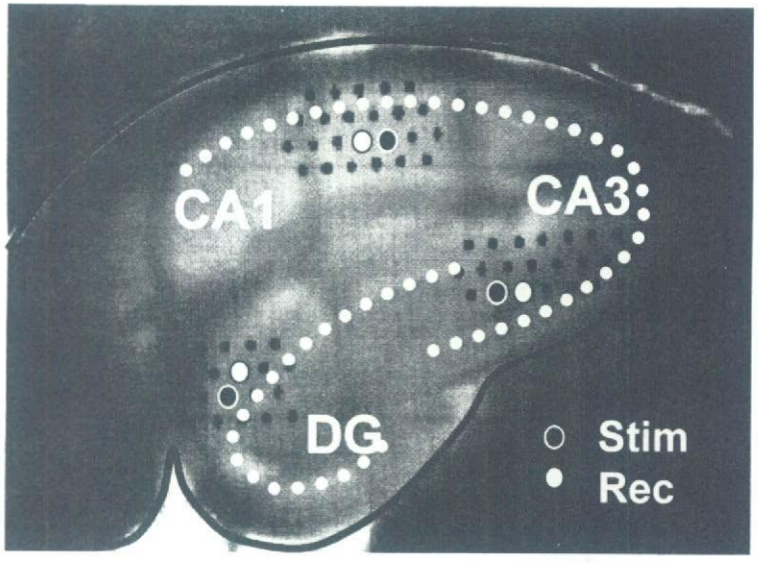

Figure S1.
The arrangement of stimulation electrodes (black circle) and recording electrodes (white circle) on a custom multielectrode probe (dotted line represent pyramidal and granule cell layers).

Fig. S2

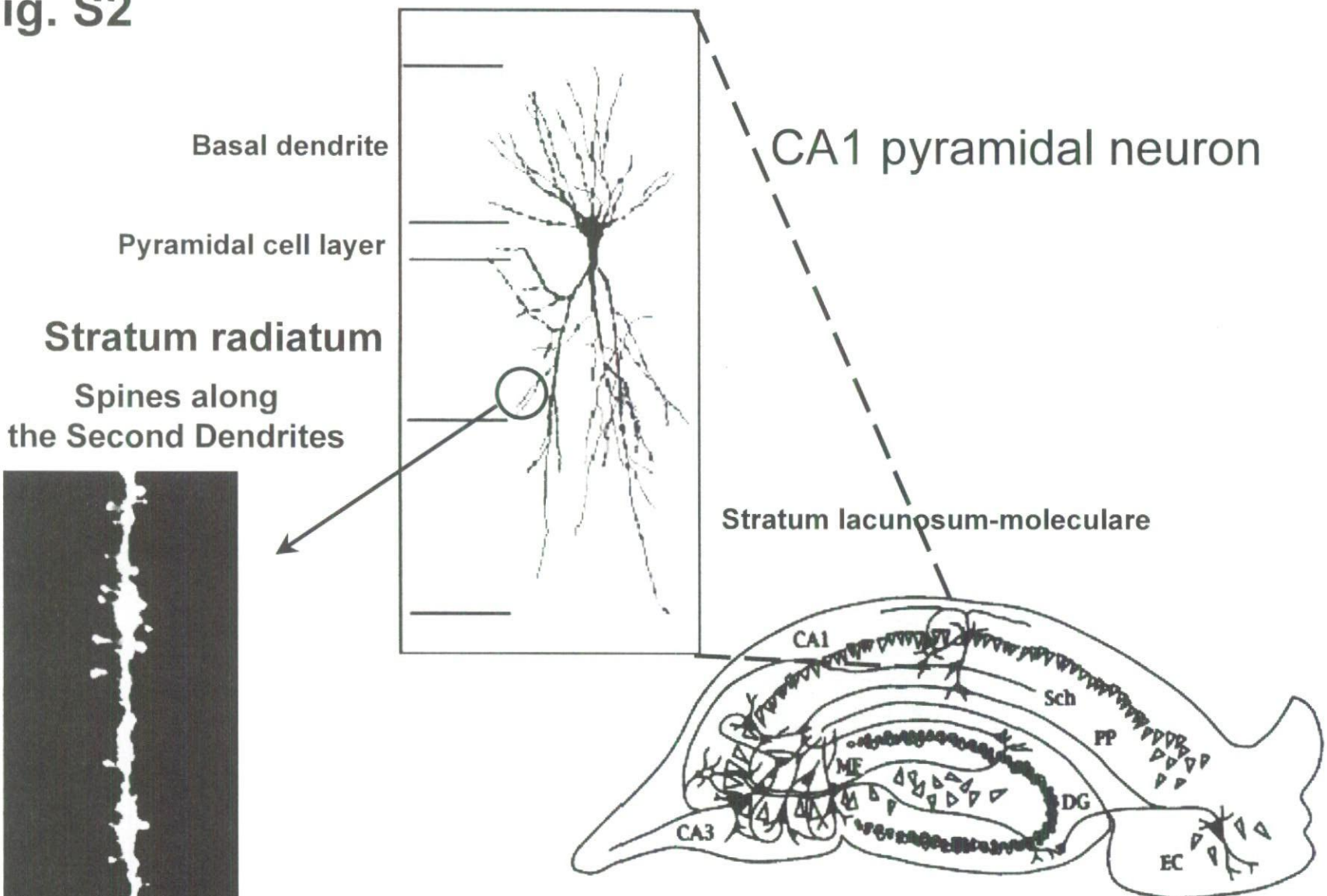

Figure S2.
Schematic illustration for diagram of the spine analysis.

Fig. S3

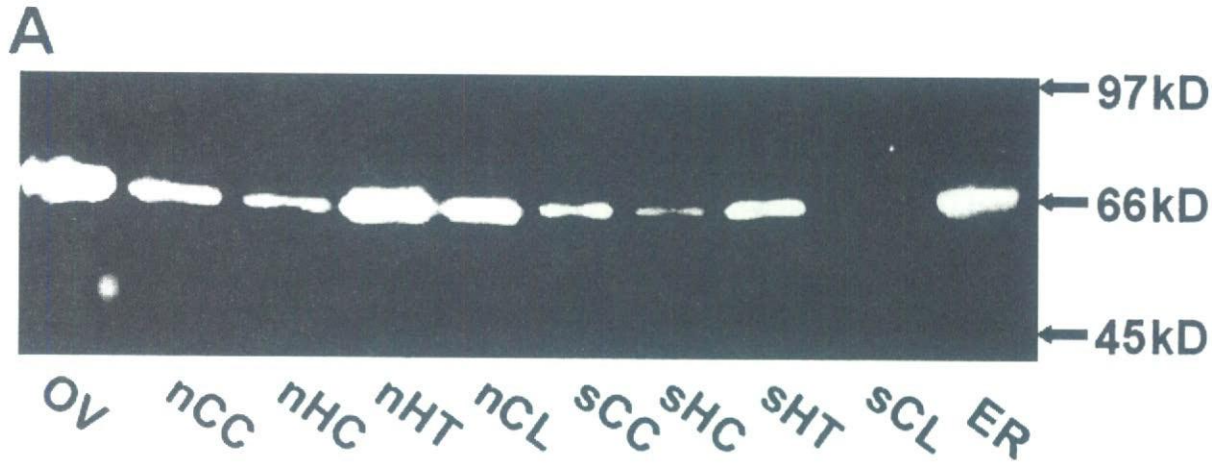

Figure S3.

(A)Blot with RC-19 antibody of the nuclear and synaptosomal fractions from adult rat brain. From left to right: homogenates of ovary (OV), nuclear fractions of cerebral cortex (nCC), hippocampus (nHC), hypothalamus (nHT), cerebellum (nCL). synaptosomal fractions of cerebral cortex (sCC), hippocampus (sHC), hypothalamus (sHT), cerebellum (sCL), and ERα expressed in COS-7 cells (ER).

Fig. S3

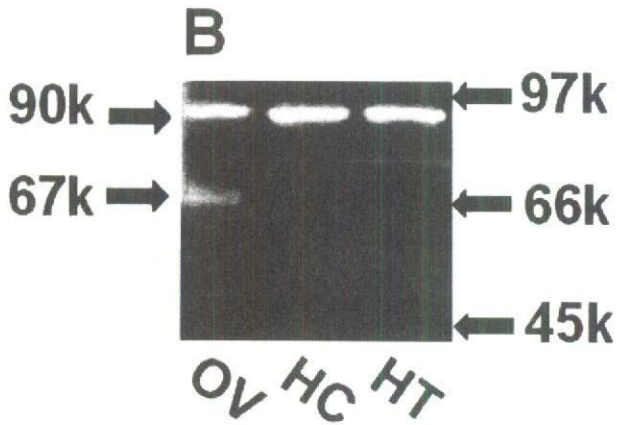

Figure S3.
(B) Staining with AS409 antiserum of tissue homogenates from adult rat. From left to right, OV from 4 week rat, HC, and HT. Representative blots are shown, but several independent experiments are performed for each blot. Molecular weights (97, 66, 45, 38 kDa) indicated in the figure are taken from molecular weight standard proteins.

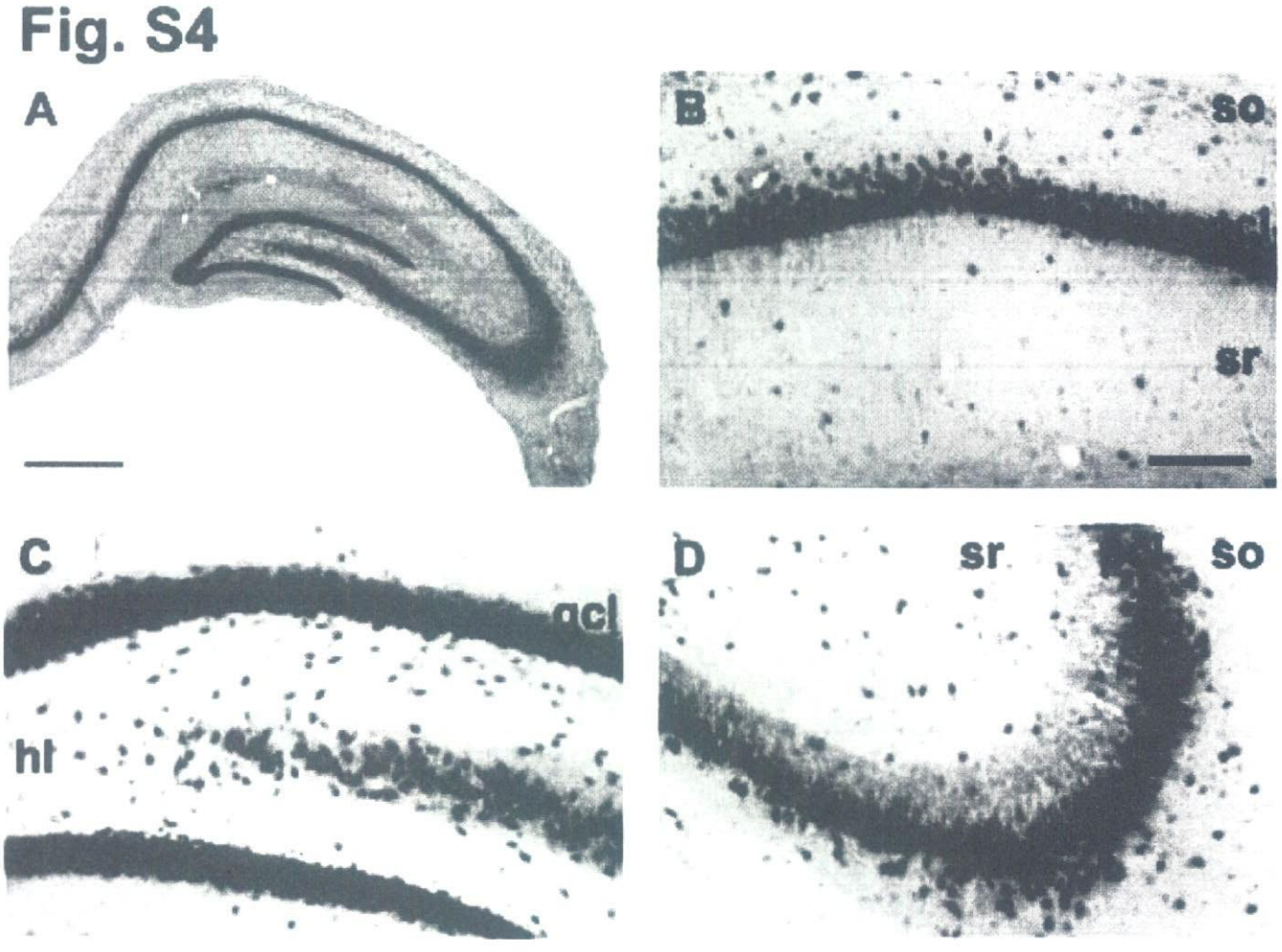

Figure S4.
Immunohistochemical staining with MC-20 antiserum in the hippocampal slices of adult male rat (A-D). (A) the coronal section of the whole hippocampal formation. (B) CA1 region. (C) dentate gyrus. (D) CA3 region. so, stratum oriens; pcl, pyramidal cell layer; sr, stratum radiatum; gcl, granule cell layer; hl, hilus. Scale bar, 500 μm for (A), and 200 μm for (B)-(D).

Fig. S5

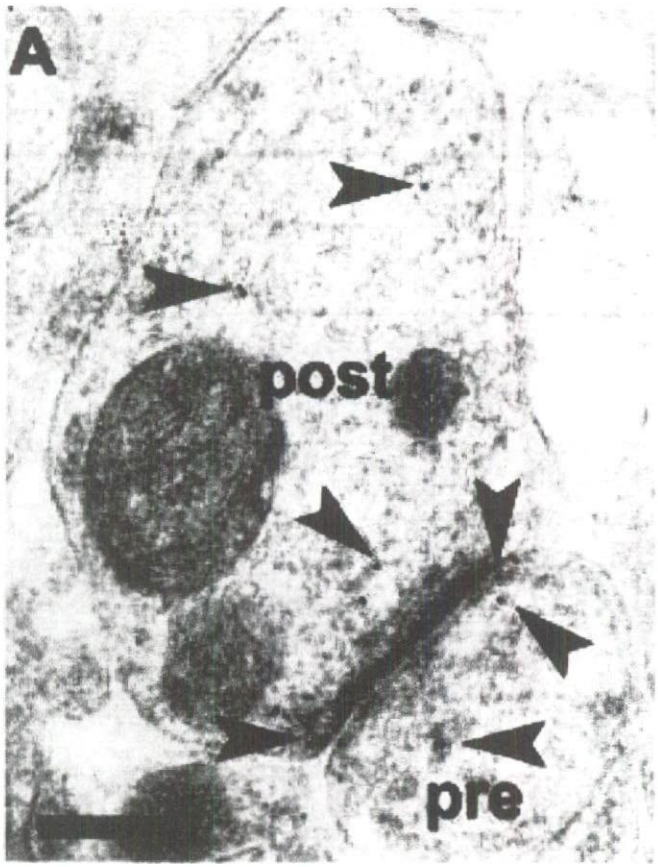

Fig. S5

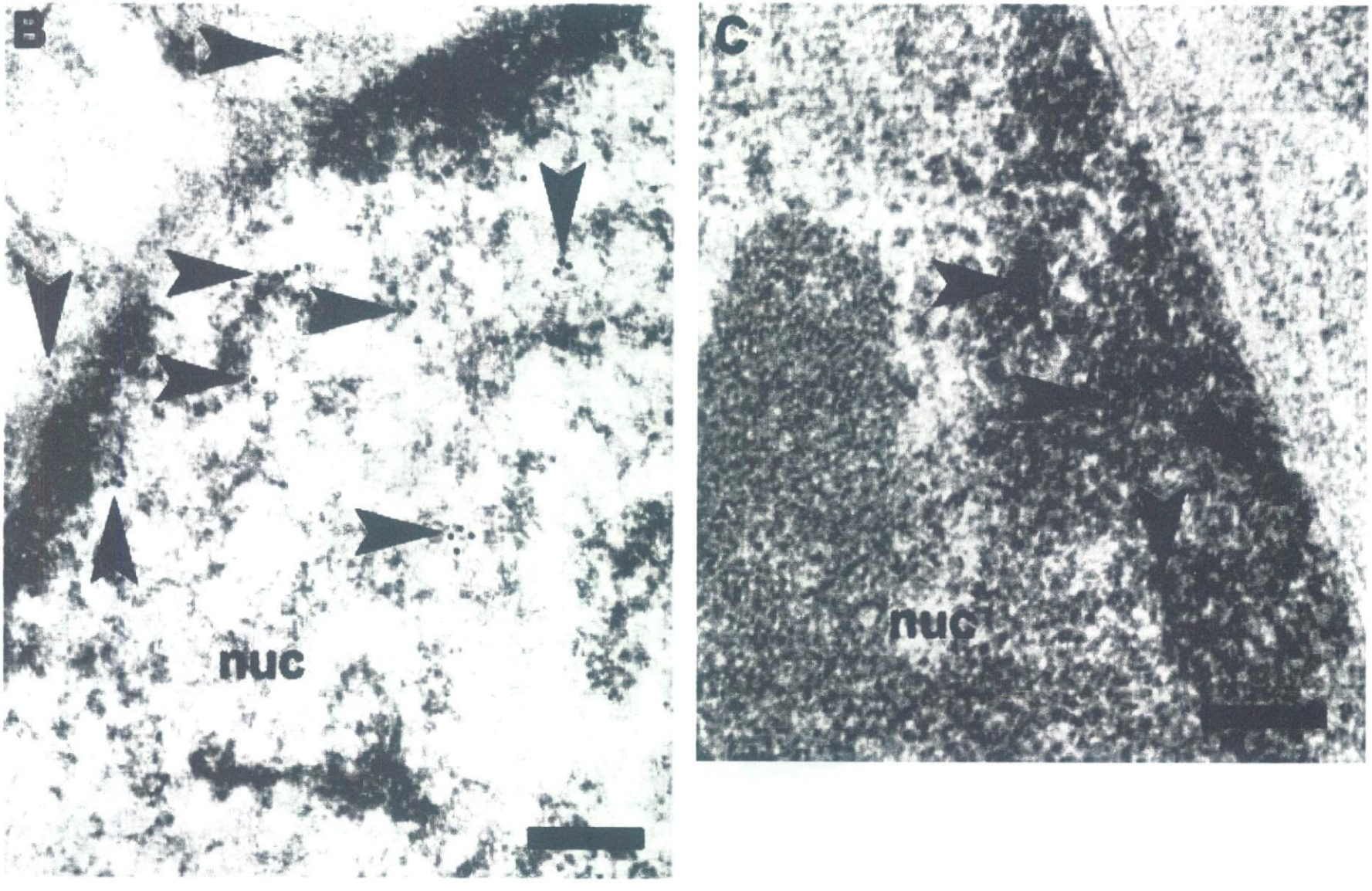

Fig. S5

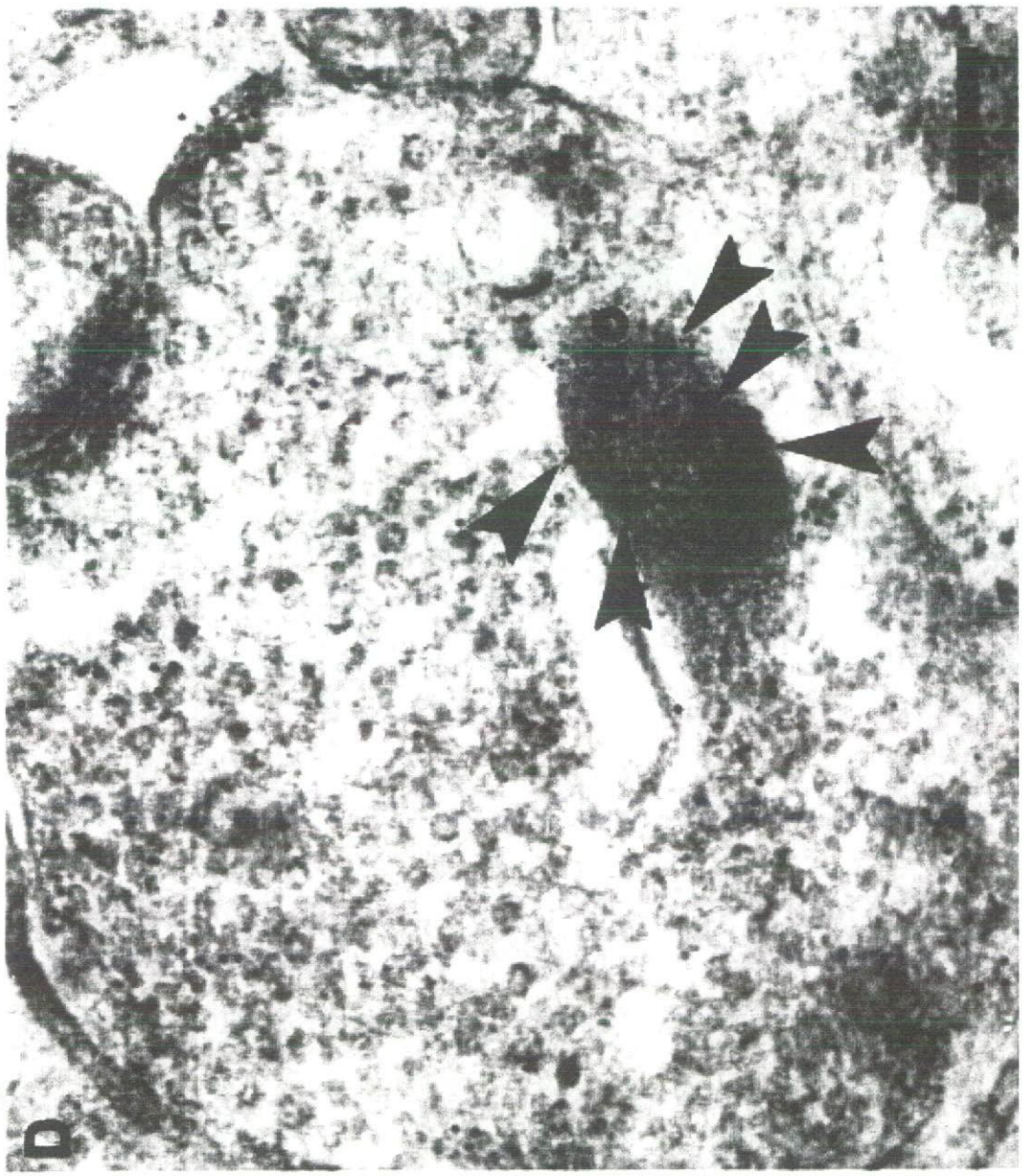

Figure S5.

Immunoelectron microscopic analysis, using RC-19 antibody, of the distribution of ERα within synapse of stratum radiatum of CA3 neuron (A), nucleus of CA3 neuron (B), and nucleus of DG (C) regions. A 1:1000 dilution of RC-19 was used to prevent nonspecific labeling. pre, presynaptic region; post, postsynaptic region. Scale bar, 200 nm.

(D) Immunoelectron microscopic analysis, using MC-20 antiserum, of the distribution of antigens of MC-20 in the presynaptic regions, in the stratum radiatum of the hippocampal CA3 region. Heavy staining was observed and several gold particles (arrowheads) were associated with the mitochondria (mito). Scale bar, 200 nm.

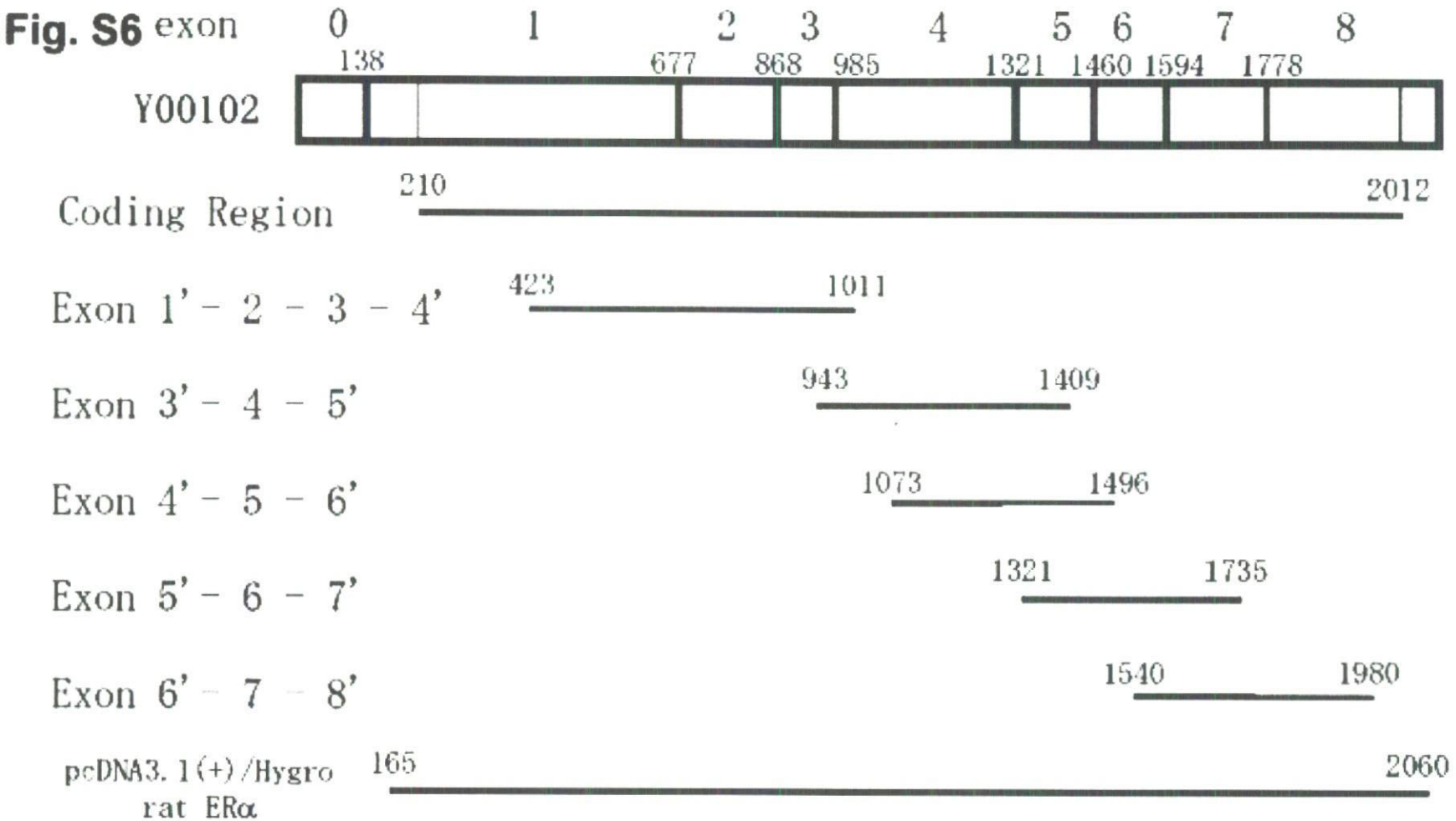

Figure S6.

The distribution of the following subregions of ERα mRNA amplified with specific primer pairs: Exon 1'-2-3-4', Exon 3'-4-5', Exon 4'-5-6', Exon 5'-6-7', and Exon 6'-7-8'.

Fig. S7

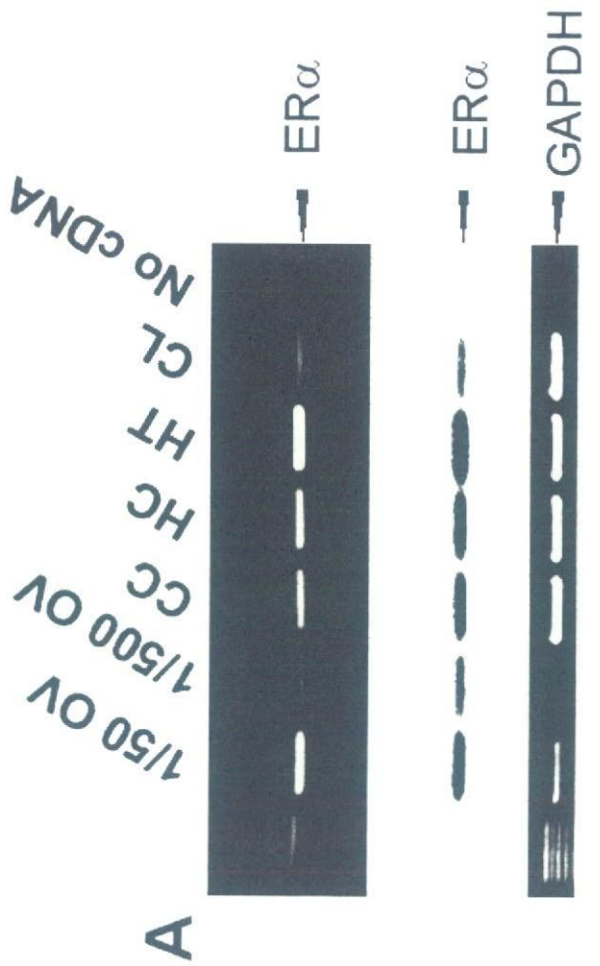

Fig. S7

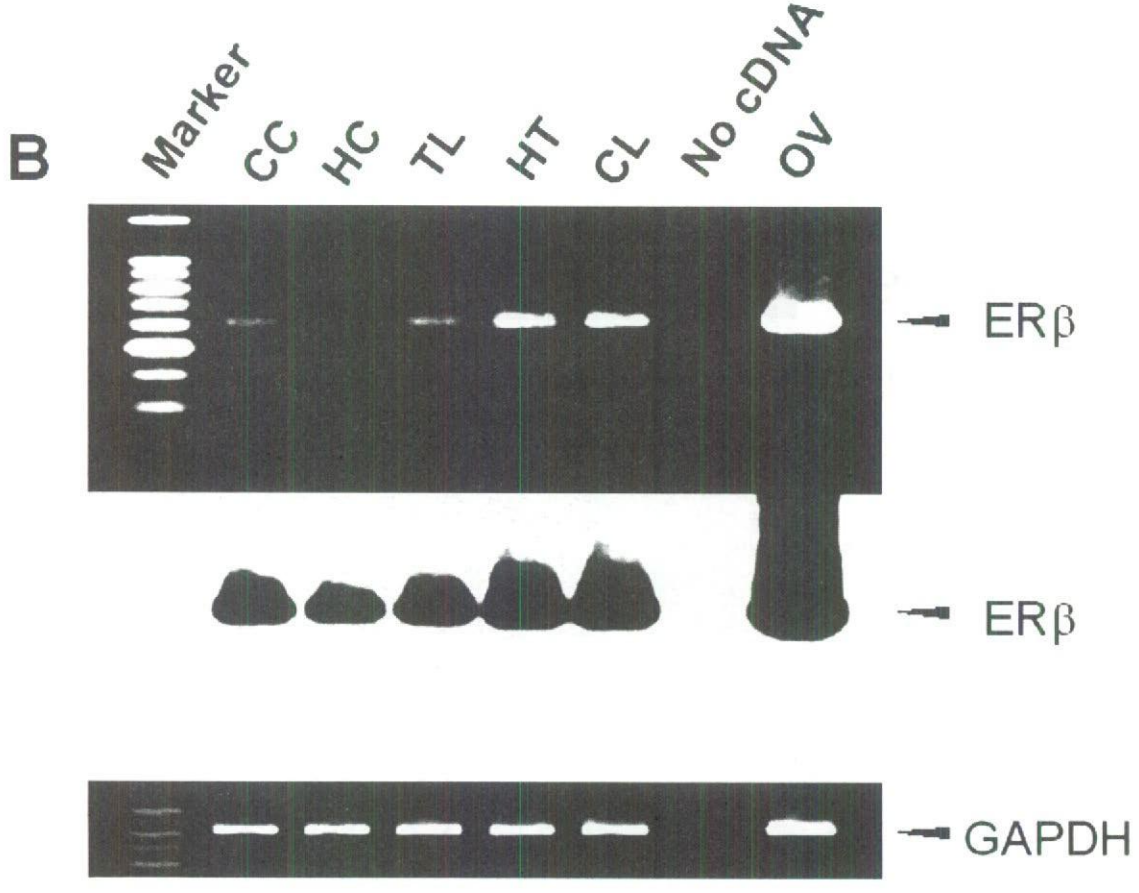

Figure S7.

(A) RT-PCR analysis of mRNAs for ERα expressed in the brain subregions. RT-PCR products for mRNAs (50 ng each) of ERα were electrophoresed on 1.5% agarose gel, and visualized with ethidium bromide. (Top) From left to right, size marker (Marker), ovary diluted at 1/50 (1/50 OV), ovary diluted at 1/500 (1/500 OV), cerebral cortex (CC), hippocampus (HC), hypothalamus (HT), cerebellum (CL), no cDNAs (No cDNA) as a negative control. (Middle) Southern hybridizations. (Bottom) The ethidium bromide staining of GAPDH. The PCR cycles are 34 cycles.

(B) RT-PCR analysis of mRNAs for ERβ expressed in the brain subregions. RT-PCR products for mRNAs (50 ng each) of ERβ were electrophoresed on 1.5% agarose gel, and visualized with ethidium bromide. (Top) From left to right, size marker (Marker), cerebral cortex (CC), hippocampus (HC), thalamus (TL), hypothalamus (HT), cerebellum (CL), no cDNAs (No cDNA) as a negative control, and ovary (OV). (Middle) Southern hybridizations. (Bottom) The ethidium bromide staining of GAPDH. The PCR cycles are 36.

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BRAIN RESEARCH REVIEWS

Review

Rapid modulation of synaptic plasticity by estrogens as well as endocrine disrupters in hippocampal neurons

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ABSTRACT

Estrogen modulates memory-related synaptic plasticity not only slowly but also rapidly in the hippocampus. However, molecular mechanisms of the rapid action are yet largely unknown. We here describe rapid modulation of representative synaptic plasticity, i.e., long-term depression (LTD), long-term potentiation (LTP) and spinogenesis, by 17beta-estradiol, selective estrogen agonists as well as endocrine disrupters.

The authors demonstrated that 1–10 nM estradiol induced rapid enhancement of LTD within 1 h in not only CA1 but also CA3 and dentate gyrus (DG). On the other hand, the modulation of LTP by estradiol was not statistically significant.

The total density of spines was increased in CA1 pyramidal neurons, within 2 h after application of estradiol. The total density of thorns (postsynaptic spine-like structure) was, however, decreased by estradiol in CA3 pyramidal neurons. Both the increase of spines in CA1 and the decrease of thorns in CA3 were completely suppressed by Erk MAP kinase inhibitor. Only ERalpha agonist PPT induced the same enhancement/suppression effect as estradiol on both LTD and spinogenesis in CA1 and CA3. ERbeta agonist DPN induced completely different results.

ERalpha localized in spines and presynapses of principal glutamatergic neurons in CA1, CA3 and DG. The same ERalpha was also located in nuclei and cytoplasm. Identification of ERalpha was successfully performed using purified RC-19 antibody. Non-purified ERalpha antisera, however, reacted significantly with unknown proteins, resulting in wrong immunostaining different from real ERalpha distribution.

An issue of 'endocrine disrupters' (1–100 nM low dose of environmental chemicals), which are artificial xenoestrogenic or anti-xenoestrogenic substances, has emerged as a

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Abbreviations: BPA, bisphenol A; CNQX, cyano-nitroquinoxaline-dione; DES, diethylstilbestrol; DPN, diarylpropionitrile; LTD, long-term depression; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate; NP, 4-nonylphenol; PPT, propyl-pyrazole-trinyl-pheno

[1] Contributed equally to the present work.

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social and environmental problem. Endocrine disrupters were found to significantly modulate LTD and spinogenesis. Bisphenol A (BPA) and diethylstilbestrol (DES) enhanced LTD in CA1 and CA3. The total spine density was significantly increased by BPA and DES in CA1. Most probable receptors for BPA and DES may be Ralpha; however, other receptors might also be involved.

Contents

1. Introduction

Estradiol exerts rapid (e.g., 1 h) influence on the synaptic plasticity of rat hippocampal glutamatergic neurons in slices, as has been demonstrated by a number of electrophysiological investigations in rats and mice, concerning the long-term potentiation (LTP) in CA1 (Balthazart and Ball, 2000; Foy et al., 1999), the long-term depression (LTD) in CA1 (Vouimba et al., 2000) or kainate current in CA1 (Gu and Moss, 1996; Gu et al., 1999). To explain this modulation, attempts have been made to identify synaptic/membrane estrogen receptors in the hippocampus (Mukai et al., 2007). On the other hand, extensive studies have been performed to investigate the role of estrogens in slowly (1–4 days) modulating hippocampal plasticity, because the hippocampus is known to be a target for the actions of gonadal estrogens reaching the brain via the circulation. For example, the density of dendritic spines in the CA1 pyramidal neurons is modulated *in vivo* by estrogen replacement in ovariectomized animals (Gould et al., 1990; MacLusky et al., 2005; Woolley et al., 1990; Woolley and McEwen, 1992) and androgens in castrated animals (MacLusky et al., 2005), resulting in increase/recovery of the number of spines and spine-synapses.

The site of estrogen action in the hippocampus is a matter of debate for more than a decade. So far, two distinct types of estrogen receptor have been identified in the mammalian brain: ERα (McEwen, 2002; Simerly et al., 1990) and ERβ (Mitra et al., 2003; Shughrue et al., 1997). The rapid effect of estrogen may be achieved by either ERα or ERβ possibly localized at the membrane, in analogy with cultured cells of peripheral origin (McEwen and Alves, 1999; Razandi et al., 1999). Subcellular and cellular localization of estrogen receptors is still not fully elucidated even for ERα, particularly in adult rat hippocampus. Many studies have reported in female rats that ERα immunoreactivity has been found in the nuclei of scattered inhibitory gamma-aminobutyric acid (GABA)ergic interneurons by light or electron microscopy using AS409 antiserum against ERα (Milner et al., 2001; Orikasa et al., 2000; Woolley et al., 1997). It is therefore assumed that interneurons are the targets of estrogen action.

In contrast, we have been exploring the possibility that estrogen may exert its effects directly on principal neurons, because of growing evidence such as an NMDA receptor-dependent mechanism of estradiol regulation on dendritic spine density (Woolley and McEwen, 1994), and increase of glutamate binding to NMDA receptors by estradiol (Woolley et al., 1997). Recently, we successfully demonstrated that 17β-estradiol enhanced the long-term depression (LTD) as well as new spinogenesis within 1–2 h estradiol treatments of the adult rat hippocampus (Ishii et al., 2006). We also successfully determined the synaptic localization of ERα which may predominantly catalyze these modulations. In considering the role of estrogen in memory processing, its effect on LTD is essential. LTD is not simply a "forgetting" mechanism, but LTD may be a positive mechanism used to "correct" wrong memories formed by initial LTP processes which store not only correct information but also wrong information (Migaud et al., 1998). Regulation of spinogenesis is another important role of estrogen in memory processes due to serving new spines for creating new synapses.

Because the memory-related synaptic plasticity is modulated by estradiol, it is reasonable to postulate that orally administered estrogen-like endocrine disrupters (i.e., low dose of environmental chemicals) might also affect synaptic plasticity (Kawato, 2004), when reaching neurons via the blood circulation and by crossing the blood–brain barrier. Bisphenol A (BPA) is suspected to disturb estrogen functions in the brain tissues, since BPA has been shown to reach the brain of both mother and fetus within 1 h after s.c. injection to mother rat (Uchida et al., 2002). The time required for BPA to reach the brain was not significantly different from that required to reach other peripheral organs. In contrast to the efficient detoxification of endocrine disrupters in the liver, detoxification in the brain may be much less efficient, due to the extremely low level of drug-metabolizing enzymes (e.g., cytochrome P450s) in the brain (Chinta et al., 2005; Hojo et al., 2004; Kishimoto et al., 2004; Miksys and Tyndale, 2002). These findings suggest that endocrine disrupters actually reach mammalian brains (including human brains) and then disrupt their functions. We here demonstrate the rapid effects of 10–100 nM endocrine disrupters such as bisphenol A (BPA), diethylstilbestrol (DES) and 4-nonylphenol (NP) on LTD and spinogenesis.

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2. Rapid modulation of synaptic plasticity by estrogens

2.1. *LTD and LTP*

17β-Estradiol may rapidly modulate two different types of synaptic plasticity of neurons. One is synaptic transmission such as LTD or LTP, and the other is spinogenesis. LTD and LTP probe the characteristics of preformed synapses, whereas spinogenesis analyzes not only spine-synapses (spines forming synapses) but also free spines (spines without forming synapses). Estradiol-induced modulation of LTD or LTP occurs only in preexistent synapses, because newly generated spines by estradiol treatments do not form new synapses within 2 h, as judged from no increase in the baseline magnitude of EPSP signal during 2 h of estradiol perfusion (Mukai et al., 2007).

Evidence is emerging that estradiol exerts a rapid influence (0.5–1 h) on synaptic transmission of hippocampal slices from adult rats, as demonstrated by electrophysiology (Foy et al., 1999; Gu and Moss, 1996; Ito et al., 1999; Shibuya et al., 2003; Teyler et al., 1980). In case of the occasionally observed enhancement of LTP by 1–10 nM estradiol in CA1 pyramidal neurons, a baseline increase by 20–30% has always been observed upon the onset of 10 nM estradiol perfusion in the initial slope of the excitatory postsynaptic potential (EPSP), which has been attendant upon a further increase to approximately 160% upon high-frequency tetanic stimulation of Schaffer collaterals of hippocampus from adult rat (3 months) (Fig. 1) (Bi et al., 2000; Foy et al., 1999; Kawato, 2004). However, without this 20–30% baseline increase in EPSP slope (before the tetanic stimulation), the enhancement of LTP by estradiol is not apparent, with regard to the pure tetanic stimulation-induced LTP. In other words, the magnitude of pure tetanic stimulation-induced LTP (approximately 130%) is nearly the same between the presence and the absence of 10 nM estradiol (Fig. 1) (Ito et al., 1999; Kawato, 2004). It should be noted that in 3–4 weeks rats, 10 nM estradiol even suppressed LTP-induction down to the same level as that for adult rats (Ito et al., 1999; Shibuya et al., 2003). Estradiol effects on LTP seem to be significantly dependent on the age of rats.

In memory processing, not only LTP (memory forming mechanism) but also LTD is essential. Mutant mice, which show enhanced LTP and suppressed LTD, have shown impaired learning of Morris water maze (Migaud et al., 1998). This suggests that LTD may be required to "correct" wrong memories formed by initial LTP processes which store not only correct information but also wrong information.

We found that LTD was very sensitive to 17β-estradiol treatments in hippocampal slices from adult male rats. We demonstrated, for the first time, a significant rapid enhancement of LTD by 1–10 nM estradiol perfusion in CA1, CA3 and dentate gyrus (DG) (Fig. 2) (Mukai et al., 2007). Recordings were performed using 64 planar multielectrodes particularly arranged to stimulate the Schaffer collaterals in the stratum radiatum of CA1, the recurrent collateral fibers in the stratum radiatum of CA3, and the medial perforant pathways in the molecular layer of DG. LTD was induced pharmacologically by the transient application (3 min) of NMDA. This LTD was induced by the activation of phosphatase due to a moderate Ca^{2+} influx through NMDA receptors (Lee et al., 1998). The plateau EPSP amplitude at 60 min after NMDA application was 80.4% (CA1), 88.8% (CA3) and 95.1% (DG), respectively. A 30 min preperfusion of 10 nM estradiol significantly enhanced LTD resulting in the residual EPSP amplitude at 60 min of 59.7% (CA1), 79.1% (CA3) and 92.2% (DG) (Fig. 2) (Mukai et al., 2007). Investigations using specific estrogen agonists indicated that the contribution of ERα (but not ERβ) was essential to these estradiol effects. Propyl-pyrazole-trinyl-phenol (PPT, ERα agonist) (Harrington et al., 2003) at 100 nM exhibited a significant LTD enhancement in CA1, while diarylpropionitrile (DPN, ERβ agonist) (Harrington et al., 2003) did induce a suppression of LTD in CA1, implying that the contribution of ERβ was opposite to that of ERα in the estradiol effect on LTD. Taken collectively, estradiol-bound ERα may activate phosphatase at moderate Ca^{2+} concentration of around 0.7–1 μM upon 30 μM NMDA application (Yang et al., 1999), and facilitated dephosphorylation of AMPA receptors may induce enhancement of LTD. On the other hand, estradiol-bound ERα is not functional in LTP modulation at high Ca^{2+} concentration of around 5–12 μM under tetanic stimulation (Ishii et al., 2006; Lisman, 1989; Yang et al., 1999), because phosphorylation of AMPA receptors by CaM kinase II is a dominant process at this high Ca^{2+} concentration.

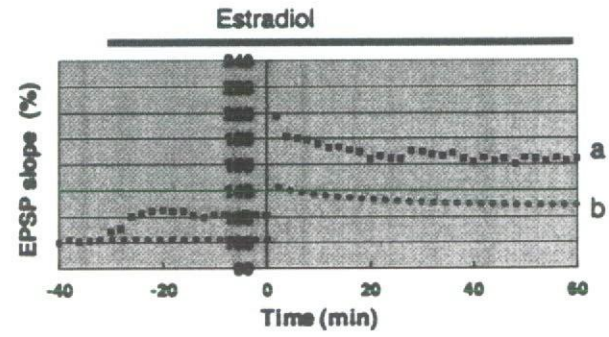

Fig. 1 – Rapid modulation of LTP by 17β-estradiol in CA1 of hippocampal slices from adult male rats. In some slices such as curve a (blue square, n=5) (observed for less than 5 slices out of 100 slices), preperfusion of 10 nM estradiol for 30 min at 30 °C increased the baseline slope of the excitatory postsynaptic potential (EPSP) to approximately 120–130%. Upon tetanic stimulation (100 Hz, 1 s, at t=0) of the Schaffer collaterals, EPSP slope was significantly increased to the final level of 164.4±12.6% (LTP-induction). In many slices such as curve b (red circle, n=6), when an increase in the baseline EPSP slope did not occur by perfusion of 10 nM estradiol (observed for nearly 95 slices out of 100 slices), EPSP slope was increased to 132.1±7.8% upon tetanic stimulation. The difference between curves a and b is primarily due to approximately 20–30% increase in the baseline EPSP slope of curve a, upon estradiol perfusion. Red bar above the graph indicates period of time during which estradiol was administered. Acute slices from adult male (3 months) Wistar rats were investigated with a conventional electrophysiological setup. [Modified from Kawato (2004)].

2.2. *Spinogenesis*

Modulation of spinogenesis is another essential action of estrogen in memory processes, involving production of new

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