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17 β -Estradiol Enhances NMDA Receptor-Mediated EPSPs and Long-Term Potentiation

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Foy, M. R., J. Xu, X. Xie, R. D. Brinton, R. F. Thompson, and T. W. Berger. 17 β -estradiol enhances NMDA receptor-mediated EPSPs and long-term potentiation. *J. Neurophysiol.* 81: 925–929, 1999. Gonadal steroid hormones influence CNS functioning through a variety of different mechanisms. To test the hypothesis that estrogen modulates synaptic plasticity in the hippocampus, *in vitro* hippocampal slices from 2-mo-old Sprague-Dawley male rats were used to determine the effect of 17 β -estradiol on both *N*-methyl-D-aspartate (NMDA) receptor-mediated excitatory postsynaptic potentials (EPSPs) through intracellular recordings and long-term potentiation (LTP) through extracellular recordings. Intracellular EPSPs and extracellular field EPSPs (fEPSPs) were recorded from CA1 pyramidal cells by stimulating Schaffer collateral fibers. In intracellular experiments, slices were perfused with medium containing bicuculline (5 μ M) and low Mg²⁺ (0.1 mM) to enhance the NMDA receptor-mediated currents and 6,7-dinitroquinoline-2,3-dione (DNQX) (10 μ M) to block the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor-mediated component. The effects of 17 β -estradiol on NMDA receptor-mediated activity were excitatory; concentrations >10 nM induced seizure activity, and lower concentrations (1 nM) markedly increased the amplitude of NMDA-mediated EPSPs (both the first and second responses increased during paired pulse stimulation by 180 and 197%, respectively). In extracellular experiments, slices perfused with 17 β -estradiol (100 pM) exhibited a pronounced, persisting, and significant enhancement of LTP of both the fEPSP slope (192%) and fEPSP amplitude (177%) compared with control slices (fEPSP slope = 155%; fEPSP amplitude = 156%) 30 min after high-frequency stimulation. These data demonstrate that estrogen enhances NMDA receptor-mediated currents and promotes an enhancement of LTP magnitude.

INTRODUCTION

Estrogenic steroids are reported to alter electrophysiological, biochemical, and morphological properties of mammalian CNS neurons and glial cells (Brinton 1993; Brinton et al. 1997a,b; Gould et al. 1990; Murphy and Segal 1996; Simerly et al. 1990; Stone et al. 1998; Wong and Moss 1991; Woolley et al. 1990). Although modification of gene expression as a consequence of estrogen liganding to DNA-binding receptors is the traditional framework for interpreting underlying mechanisms, an increasing number of reports document effects of acute application of estrogenic steroids that are too rapid (occurring within ≤ 10 min) to be accounted for by a genomic pathway. In particular, estrogenic steroid-induced changes in

neuronal excitability suggest other, nongenomic mechanisms involving a direct interaction with sites of the plasma membrane to regulate ligand-gated ion channels and neurotransmitter transporters (Wong et al. 1996). Effects of estrogen on the electrophysiological activity of rodent hippocampal neurons were first reported by Teyler et al., who found that 17 β -estradiol treatment induced a rapid (<10 min) enhancement of glutamatergic synaptic transmission in the CA1 region of *in vitro* hippocampal slices (Teyler et al. 1980). Subsequent reports indicated that only the biologically active isomer of estrogen, 17 β -estradiol, and not the 17 α -estradiol isomer is effective in eliciting these short-term electrophysiological effects (Foy and Teyler 1983; Wong and Moss 1991, 1992). On the basis of intracellular *in vitro* recordings from CA1 pyramidal cells, Wong and Moss (1992) reported that administration of 17 β -estradiol increased synaptic excitability by enhancing the magnitude of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor-mediated responses. The rapid onset of increased excitability and its blockade by 6-cyano-7-nitroquinaxaline-2,3-dione (CNQX, an AMPA receptor antagonist) and not D-2-amino-5-phosphonovalerate [D-APV, a competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist] supported a postsynaptic membrane site of action and an expression by non-NMDA receptor-channels. Later studies with whole cell recordings found that acute 17 β -estradiol application potentiated kainate-induced currents in a subpopulation (38%) of CA1 cells (Gu and Moss 1996), although a direct interaction between 17 β -estradiol and the receptor channel was not indicated (Wong and Moss 1994). In total, the work of Moss and colleagues supports the possibility of a second messenger mechanism underlying the rapid effects of 17 β -estradiol, most likely involving a G-protein coupled AMPA-dependent phosphorylation event.

The apparently exclusive estrogenic steroid modification of non-NMDA receptor channels stands in contrast to a large body of evidence demonstrating 17 β -estradiol regulation of NMDA receptor-mediated function. Morphological studies on the course of neuronal development conducted *in vitro* in our laboratory (Brinton et al. 1997a,b) have shown that estrogenic steroids exert a growth-promoting, neurotrophic effect on hippocampal and cortical neurons via a mechanism that requires activation of NMDA receptors. Moreover, the neurotrophic effects of estrogenic steroids can be blocked by an NMDA receptor antagonist in cultured neurons before synaptic contacts occur (Brinton et al. 1997b). *In vivo* studies by Woolley and McEwen (1994) revealed a proliferation of dendritic spines

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after 17β -estradiol treatment that can be prevented by blockade of NMDA receptor channels, although not by AMPA or muscarinic receptor antagonists. Other reports provide evidence that chronic 17β -estradiol treatment increases the number of NMDA receptor binding sites and NMDA receptor-mediated responses (Gazzaley et al. 1996; Woolley et al. 1997).

The possibility of direct regulation of NMDA receptor-

mediated synaptic transmission by 17β -estradiol may not have been detected previously because tests of this hypothesis are so few in number and, more importantly, have yet to be conducted under optimal conditions. Because of the voltage-dependent blockade of the NMDA channel by Mg^{2+} and the slow kinetics of ligand-gated channel opening relative to that of the AMPA receptor subtype, there is only a minor NMDA receptor-mediated component of the excitatory postsynaptic potential (EPSP) evoked by low-frequency stimulation of glutamatergic afferents. This NMDA component can be enhanced with low Mg^{2+} concentration or high-frequency stimulation to induce the depolarization accompanying the summation of overlapping EPSPs (Xie et al. 1992). In the experiments reported here, we used both the conditions of low Mg^{2+} and high-frequency stimulation in separate experiments to examine the acute effects of 17β -estradiol on pharmacologically isolated NMDA receptor-mediated EPSPs in CA1 pyramidal cells to determine if estradiol alters NMDA receptor-channel activity. In other experiments, we investigated the acute effects of 17β -estradiol treatment on the induction and expression of long-term potentiation (LTP), an enduring enhancement of glutamatergic synaptic transmission that, in the hippocampal CA1 region, requires high-frequency stimulation sufficient to activate NMDA receptor-channels.

METHODS

Transverse hippocampal slices (400 μ m) were prepared from experimentally naive, 200- to 350-g adult male Sprague-Dawley rats (Harlan). Slices were incubated in an artificial cerebrospinal fluid (aCSF) perfusion medium that consisted of (in mM) 126 NaCl, 5 KCl, 1.25 NaH_2PO_4 , 26 $NaHCO_3$, 10 glucose, 2 $CaCl_2$, 2 $MgCl_2$, 2 ascorbic acid, bubbled with 95% O_2 -5% CO_2 and maintained at $32 \pm 0.5^\circ C$. For intracellular recordings, slices were superfused (≈ 3 ml/min) in a submerged chamber with aCSF containing bicuculline (5 μ M) and either the AMPA receptor antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) (10 μ M) and a reduced Mg^{2+} concentration (0.1 mM) to isolate NMDA receptor-mediated EPSPs or the NMDA receptor antagonist D-2-amino-5-phosphonovalerate (D-APV; 50 μ M) and a higher Mg^{2+} concentration (1 mM) to isolate AMPA receptor-mediated EPSPs. CA1 pyramidal cell EPSPs were recorded intracellularly with glass microelectrodes filled with 2 M potassium acetate (resistance: 90–150 M Ω). Depolarizing and hyperpolarizing current injections were applied for measurement of input resistance to generate voltage steps across the neuronal membrane for calculation of input resistance. Experiments were conducted only when stable intracellular recordings were obtained from neurons with a resting mem-

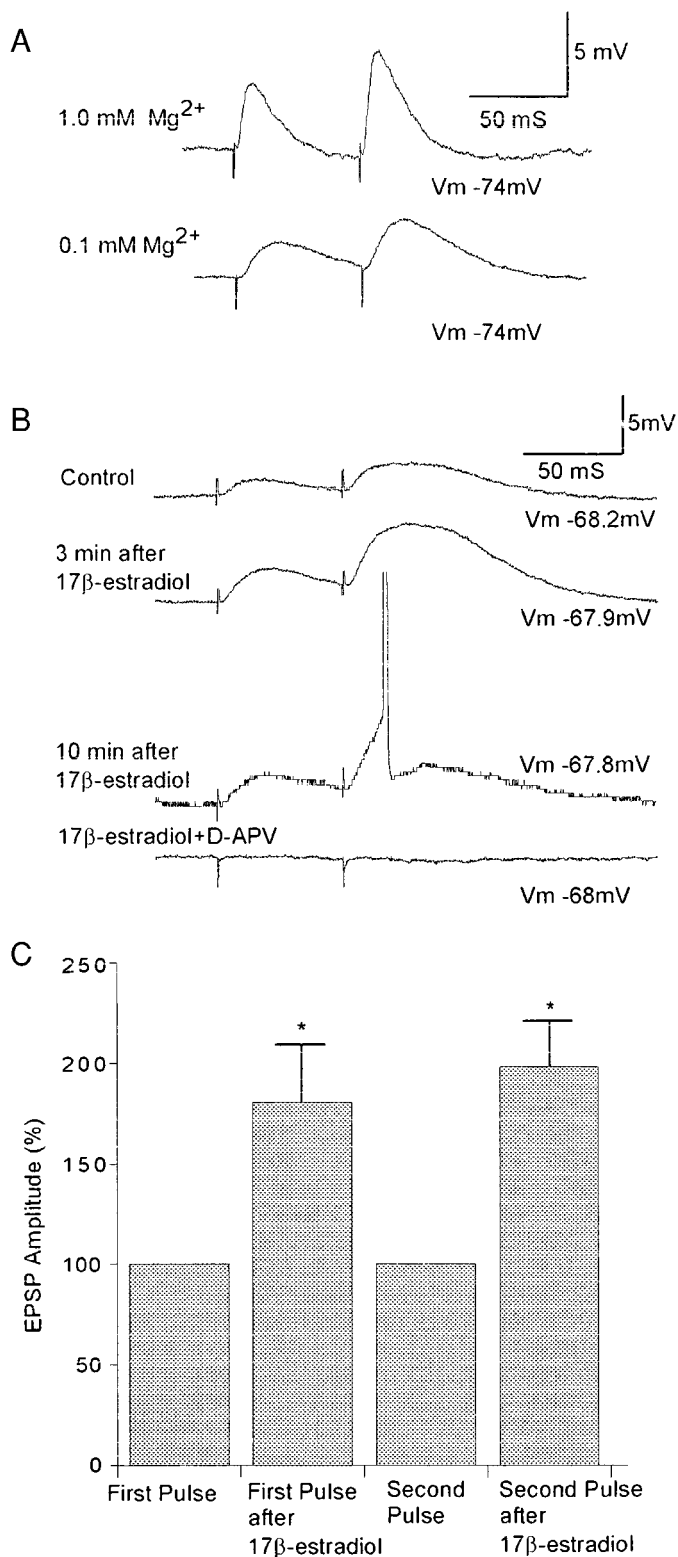


FIG. 1. The amplitude of *N*-methyl-D-aspartate (NMDA) receptor-mediated excitatory postsynaptic potentials (EPSPs) in CA1 pyramidal cells is increased shortly after the addition of 1 nM 17β -estradiol to the perfusion medium. *A*, top trace: EPSPs evoked when slice was perfused with medium including 1.0 mM Mg^{2+} and in the absence of the non-NMDA receptor antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX). Bottom trace: NMDA receptor-mediated EPSPs evoked 10 min after medium was switched to include 0.1 mM Mg^{2+} and 10 μ M of the non-NMDA receptor antagonist DNQX. *B*: 1 nM 17β -estradiol potentiated the isolated EPSPs within 3 min. In all cells potentiated (9/12), the potentiation was observed in EPSPs evoked by paired pulse stimulation and peaked within 10 min. In 5 of 9 cells, the potentiated EPSPs reached threshold and generated action potentials during 17β -estradiol perfusion. The potentiated EPSPs were blocked by the NMDA receptor antagonist D-2-amino-5-phosphonovalerate (D-APV). *C*: average amplitude of NMDA-mediated EPSPs after 17β -estradiol perfusion was increased in both EPSPs evoked by paired pulse stimulation. EPSPs from control slices were normalized, and potentiated EPSP amplitudes were extracted from recorded data after 17β -estradiol perfusion. * $P < 0.05$ ($n = 9$).

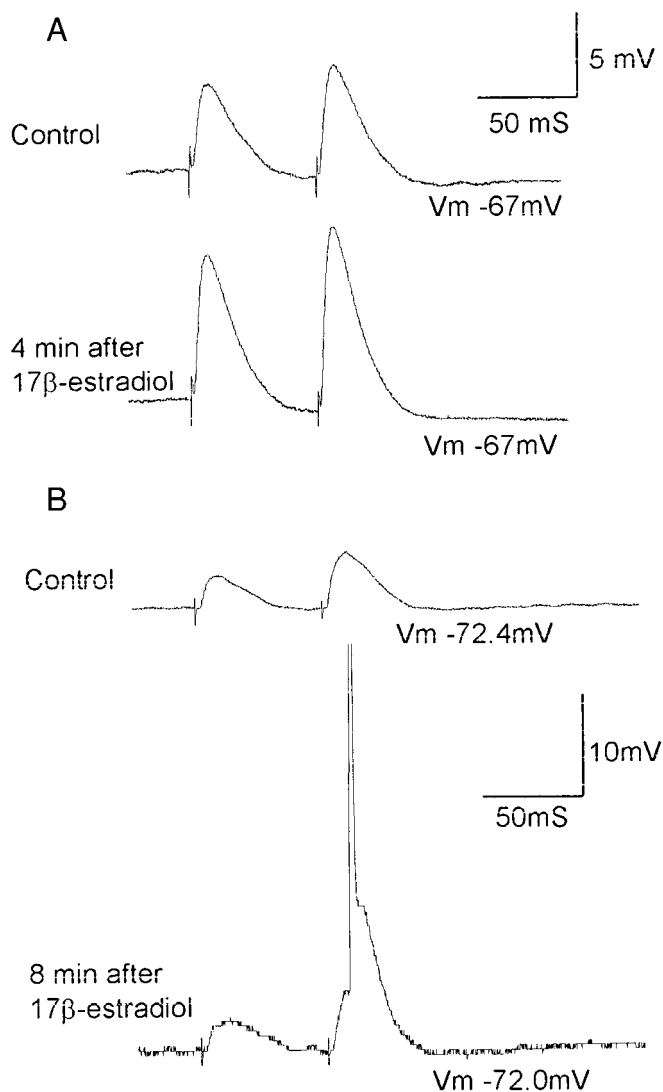


FIG. 2. Fast potentiation by 17 β -estradiol perfusion of pharmacologically isolated non-NMDA receptor-mediated EPSPs. *A*: 1 nM 17 β -estradiol potentiated the non-NMDA-mediated EPSPs in artificial cerebrospinal fluid (aCSF) containing 50 μ M D-APV and 1.0 mM Mg²⁺. *B*: some cells showed action potentials during continuous 17 β -estradiol perfusion but not in the control cells (before 17 β -estradiol perfusion).

brane potential of at least -55 mV, overshooting action potentials, and a minimum input resistance of 20 M Ω (Schwartzkroin 1975). Throughout the experiment, EPSPs were evoked via Schaffer collateral stimulation and recorded at 0.1 Hz, with 17 β -estradiol added to the aCSF incubating the slices after a stable, 10-min baseline period. In Figs. 1 and 2, each response shown is an average of 10 consecutive, individual EPSPs, except the single, individual action potential responses. For extracellular recordings, slices were maintained in an interface chamber continuously perfused (≈ 2 ml/min) for ≥ 1 h with aCSF containing 1 mM Mg²⁺. Field EPSPs (fEPSPs) were recorded from stratum radiatum of CA1 with glass microelectrodes filled with 2 M NaCl. Schaffer collateral/commissural axons were stimulated (0.05 Hz) at intensities adjusted to produce an evoked response that was 50% of the maximum recorded fEPSP for each recording with a bipolar nichrome electrode placed in the proximal stratum radiatum. After 10 min of stable, baseline fEPSP recordings, slices continued to be perfused with aCSF or aCSF containing 17 β -estradiol (Sigma Chemical) in concentrations indicated in RESULTS. The effect of 17 β -estradiol on LTP was studied with high-frequency stimulation (after

30 min of 17 β -estradiol perfusion), consisting of five trains of 100-Hz stimulation, with each train having a duration of 200 ms; the intertrain interval was 10 s. During the post-high-frequency stimulation period, fEPSPs were recorded from control slices (aCSF perfusion) and experimental slices (aCSF + 17 β -estradiol perfusion) for 30 min.

Data for both intracellular and extracellular recordings were collected and analyzed on a PC with programs written in AXOBASIC. The initial slope and amplitude of EPSPs were used in all statistical analyses, with data from different slices combined and normalized to compare recordings from the control and experimental periods. Statistical significance of differences in normalized (means \pm SE) EPSP slope and amplitudes within the previous conditions were evaluated with analyses of variance and planned two-tailed *t*-tests.

RESULTS

17 β -estradiol enhancement of NMDA receptor-mediated EPSPs

In the presence of the AMPA receptor antagonist DNQX and 0.1 mM Mg²⁺, EPSPs evoked by Schaffer collateral stimulation were prolonged in duration, with slow rise and fall times characteristic of NMDA receptor-mediated synaptic responses (Xie et al. 1992). Identification of DNQX-resistant responses as being NMDA receptor mediated was confirmed by the effects of D-APV, which completely abolished residual evoked synaptic activity (Fig. 1).

At 1 nM, 17 β -estradiol induced a rapid increase in the amplitude of the NMDA receptor-mediated EPSPs evoked by paired impulse stimulation of Schaffer collateral input in 9 of 13 cells. Measured at ~ 6 min after application of 17 β -estradiol, the enhancement occurred for both of the paired responses (Fig. 1C). The mean increase of the first response was $180 \pm 26\%$, $P < 0.05$, and that of the second response was $197 \pm 22\%$, $P < 0.01$. After correcting for the lag time of the perfusion system (~ 1.5 min), the latency for onset of the 17 β -estradiol effect was < 2 min for all cells. In some cells, the enhanced EPSPs reached the firing threshold after a longer (> 10 min) 17 β -estradiol application period (Fig. 1B). For two cells, the enhanced EPSPs were further confirmed as NMDA receptor mediated by their nearly complete blockade after bath application of 50 μ M D-APV (Fig. 1B).

In another series of experiments, the AMPA receptor was pharmacologically isolated by applying the NMDA receptor antagonist D-APV (50 μ M) to the bath. The effect of 17 β -estradiol on the AMPA receptor was then examined, and we observed potentiation of the AMPA component by 17 β -estradiol in 5 of 14 cells (36%) (Fig. 2, A and B). This result is consistent with a previous report (Wong and Moss 1991).

17 β -estradiol enhancement of LTP

Consistent with the results of intracellular studies, an increase in synaptic transmission occurred in CA1, after acute perfusion of 100 pM 17 β -estradiol onto experimental hippocampal slices (fEPSP mean increase of slope was 113% (experimental) vs. 101% (control); fEPSP mean increase of amplitude was 112% (experimental) vs. 100% (control), $F(1,180) = 229$, $P < 0.0001$, and $F(1,180) = 353$, $P < 0.0001$, respectively). Field EPSP responses of the two groups were identical during the baseline period before 17 β -estradiol perfusion [fEPSP slope and fEPSP amplitude, $F(1,58) = 0.000$, NS, and $F(1,58) = 0.000$, NS]. In Fig. 3, the two groups of

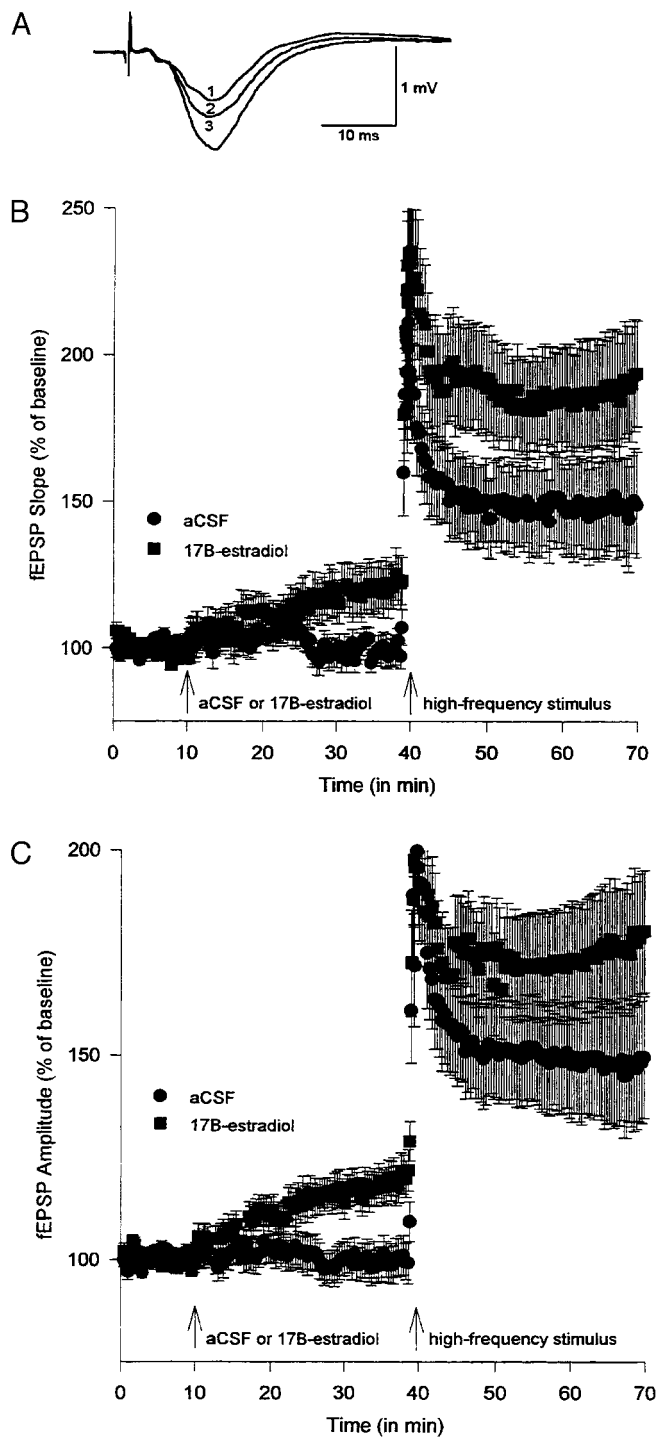


FIG. 3. Field EPSP (fEPSP) recordings in area CA1. *A*: all hippocampal slices were perfused with aCSF for 10 min to obtain fEPSP slope and amplitude percent baseline data. After 10-min of baseline recording, experimental slices were perfused with 100 pM 17 β -estradiol. Control slices continued to be perfused with aCSF. After 30 min of either 17 β -estradiol or aCSF perfusion, all slices received high-frequency stimulation, designed to induce long-term potentiation. *A1*: fEPSP recording at end of 10-min baseline period. *A2*: fEPSP recording at end of 30 min of 17 β -estradiol perfusion. *A3*: fEPSP recorded 30 min after high-frequency stimulation in slices perfused with 17 β -estradiol. *B*: fEPSP slope responses in area CA1. Data points represent averaged fEPSP slope \pm SE (taken at each 20-s sweep) for experimental (17 β -estradiol-treated) and control (aCSF) hippocampal slices. *C*: fEPSP amplitude responses in area CA1. Data points represent averaged fEPSP amplitude \pm SE (taken at each 20 s sweep) for experimental (17 β -estradiol-treated) and control (aCSF) hippocampal slices.

slices from normal, young adult male rats (17 β -estradiol-treated vs. aCSF-control) showed no significant differences in either their measured fEPSP slopes or fEPSP amplitudes over the 10-min baseline period. The increase in synaptic transmission began to develop \sim 3–4 min after 17 β -estradiol perfusion onto the experimental slices and continued throughout the 30-min perfusion period.

When LTP was assessed after high-frequency stimulation, fEPSP slopes and amplitudes were increased significantly for the 17 β -estradiol-treated slices compared with control slices. fEPSP mean increase of slope was 192% (experimental) vs. 154% (control); fEPSP mean increase of amplitude was 176% (experimental) vs. 156% (control), $F(1,200)$ 305.86, $P < 0.0001$, and $F(1,200)$ 113.58, $P < 0.0001$, respectively. Thus hippocampal slices treated with 17 β -estradiol exhibited a pronounced, persisting, and significant increase in LTP as measured by both population fEPSP slope and fEPSP amplitude recordings.

DISCUSSION

These experiments establish several fundamental characteristics of the effects of estrogen on synaptic transmission in the mammalian CNS. First, we demonstrate that estrogen acts rapidly via presumed membrane mechanisms to enhance both NMDA and AMPA receptor/channel processes in response to glutamate released from Schaffer collateral terminals. Wong and Moss (1992) reported that estradiol enhances the amplitude of EPSPs at the Schaffer collateral-CA1 synapse. They observed that the increase in EPSP amplitude remains unchanged in the presence of D-APV but was blocked by CNQX, suggesting the NMDA receptor irrelevant in regard to the effects of estradiol on synaptic transmission. However, even for AMPA receptor-mediated EPSPs, the enhancing effect of estradiol was only seen in 36% of their cells. Furthermore, the NMDA component accounts for only a small fraction of the total EPSP profile under their experimental conditions. Consequently, in such conditions, any effect of estradiol on NMDA receptor/channel function would be minimally expressed and may be undetectable. In fact, in our experiments under conditions in which a lowered extracellular concentration of Mg²⁺ was applied, estradiol led to a higher percentage enhancement of the NMDA component compared with the AMPA component (75 vs. 36%). The experimental conditions used here, i.e., pharmacological isolation of the two types of receptors, also ruled out the possibility of the enhancement of one receptor component as the result of the other. Thus estradiol seems to act on both NMDA and AMPA receptors and produce acute effects in a similar fashion. It seems unlikely that these effects are presynaptic; estrogen can induce an increase in the number of stimulus-evoked action potentials in the Schaffer collaterals or an increase in the amount of glutamate released per Schaffer collateral action potential, but this possibility was not definitely ruled out here or in earlier studies. It is not yet known whether these estrogen effects are due to an action directly on the receptors or indirectly via second messenger processes that in turn influence NMDA and AMPA receptor/channel processes.

Second, our results indicate that estradiol can both increase synaptic transmission in the hippocampus and markedly enhance LTP in CA1 neurons of adult, male rats. The enhancement of LTP after acute 17 β -estradiol application (Fig. 3) could be due to an increase in activation of NMDA receptors/

channels or an increase in AMPA receptor function. Both possibilities are consistent with our intracellular data. Whatever the mechanism, the fact is that estrogen enhances LTP in hippocampal CA1. To the extent that LTP is a mechanism involved in processes of coding and storage of information, i.e., in memory formation, estrogen enhances these processes. Indeed, the estrogen enhancement of LTP reported here suggests a possible mechanism whereby estrogen can exert its facilitatory effects on memory processes in humans. Recent clinical evidence indicates that estrogenic steroids can enhance cognitive functions in humans, particularly in postmenopausal women (Henderson et al. 1997; Kawas et al. 1997). Although the estrogen regulation of functions within the limbic system may result mostly from the classical genomic mechanism, an acute, nongenomic effect of estrogen could provide an additional short-term mechanism in modulating synaptic transmission and plasticity. Our studies demonstrate that estradiol enhances synaptic transmission through both NMDA and AMPA receptors/channels and that these enhancements may underlie its facilitatory effect on the magnitude of LTP.

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