Biochimica et Biophysica Acta 1800 (2010) 1030–1044

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Modulation of synaptic plasticity by brain estrogen in the hippocampus

Hideo Mukai [a,b,c], Tetsuya Kimoto [a,b], Yasushi Hojo [a,b,c], Suguru Kawato [a,b,c,d,*], Gen Murakami [a,c], Shimpei Higo [a], Yusuke Hatanaka [a], Mari Ogiue-Ikeda [a,d]

[a] Department of Biophysics and Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, 3-8-1 Komaba, Meguro, Tokyo 153-8902, Japan
[b] Core Research for Evolutional Science and Technology Project of Japan Science and Technology Agency, The University of Tokyo, Japan
[c] Bioinformatics Project of Japan Science and Technology Agency, The University of Tokyo, Japan
[d] Project of Special Coordinate Funds for Promoting Science and Technology, The University of Tokyo, Japan

ARTICLE INFO

Article history:
Received 17 July 2009
Received in revised form 15 October 2009
Accepted 2 November 2009
Available online 10 November 2009

Keywords:
Estradiol
Estrogen
Androgen
Neurosteroid
Synaptic plasticity
Estrogen receptor
Hippocampus
Spine
LTD
LTP

ABSTRACT

The hippocampus is a center for learning and memory as well as a target of Alzheimer's disease in aged humans. Synaptic modulation by estrogen is essential to understand the molecular mechanisms of estrogen replacement therapy. Because the local synthesis of estrogen occurs in the hippocampus of both sexes, in addition to the estrogen supply from the gonads, its functions are attracting much attention.

Hippocampal estrogen modulates memory-related synaptic plasticity not only slowly but also rapidly. Slow actions of 17β-estradiol (17β-E2) occur via classical nuclear receptors (ERα or ERβ), while rapid E2 actions occur via synapse-localized ERα or ERβ. Elevation or decrease of the E2 concentration changes rapidly the density and morphology of spines in CA1–CA3 neurons. ERα, but not ERβ, drives this enhancement/suppression of spinogenesis. Kinase networks are involved downstream of ERα. The long-term depression but not the long-term potentiation is modulated rapidly by changes of E2 level.

Determination of the E2 concentration in the hippocampus is enabled by mass-spectrometry in combination with derivatization methods. The E2 level in the hippocampus is as high as approx. 8 nM for the male and 0.5–2 nM for the female, which is much higher than that in circulation. Therefore, hippocampus-derived E2 plays a major role in modulation of synaptic plasticity.

Many hippocampal slice experiments measure the restorative effects of E2 by supplementation of E2 to E2-depleted slices. Accordingly, isolated slice experiments can be used as *in vitro* models of *in vivo* estrogen replacement therapy for ovariectomized female animals with depleted circulating estrogen.

1. Introduction

Finding of local synthesis of estrogen and androgen in the adult brain opened a new field of estrogen function in relation to the regulation of daily memory formation [1–5]. For decades, neuromodulatory actions have been extensively investigated for circulating gonadal sex hormones in the hippocampus, a center of learning and memory, because the hippocampus is a target of sex hormones [6–11]. Steroid hormones have profound effects on synaptic plasticity in the brain other than the hippocampus, such as the hypothalamus.

Modulation of dendritic spines has been extensively studied in relation to memory processes and synaptic plasticity which are regulated by neurotransmitters, because synapse is a site of memory storage and spine is a postsynaptic structure. Slow modulation of synaptogenesis or electrophysiological properties is investigated by estrogen replacement for ovariectomized female rats [6–11]. An increase of synapses or an enhancement of synaptic transmission is observed upon s.c. injection of estrogen. Slow modulation of spines (postsynaptic structures) is also observed in slice cultures [6–11]. These slow genomic effects are mediated via nuclear estrogen receptors ERα/ERβ to initiate transcription processes. The rapid effect of estradiol (E2) (within 1–2 h) also occurs by modulating spine density or electrophysiological properties of the hippocampal slices [6,7,12,13]. These rapid modulations, relating to memory formation processes, favor locally synthesized steroids rather than circulating gonadal hormones which travel a long distance before reaching the brain. Rather than being a limiting factor, a weak activity of sex steroid production in the hippocampus is sufficient for the local usage within small neurons (i.e., an intracrine system). This intracrine system

Abbreviations: ACSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; DHEA, dehydroepiandrosterone; DPN, diarylpropionitrile; DHT, dihydrotestosterone; 17β-estradiol, E2; estrone, E1; GPR30, G protein coupled receptor 30; HSD, hydroxysteroid dehydrogenase; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LTD, long-term depression; LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartate; PSD, postsynaptic density; PREG, pregnenolone; PPT, propyl-pyrazole-triyl)tris-phenol; RIA, radioimmunoassay; StAR, steroidogenic acute regulatory protein; T, testosterone

* Corresponding author. Department of Biophysics and Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, 3-8-1 Komaba, Meguro, Tokyo 153-8902, Japan. Tel./fax: +81 3 5454 6517.
E-mail address: kawato@phys.c.u-tokyo.ac.jp (S. Kawato).

0304-4165/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbagen.2009.11.002

contrasts with the endocrine organs in which high expression levels of steroidogenic enzymes are necessary to supply steroids to many other organs via the blood circulation. For brain-derived sex hormones, the essential functions may be the rapid and continuous modulation of synaptic plasticity and cognitive functions.

The administration of a several-years therapy with estrogen for female patients with Alzheimer's disease following menopause is shown to be very effective in improving their capacity for learning and memory [14–17]. WHI (Women's Health Initiative) investigations with randomized methods, however, yielded contradictory results