УДК 612.44.018:616.893-053.8-092.9

The effects of ovariectomy and parathyroidectomy on synaptic activity of rat's hippocampal neurons

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Key words: ovariectomy, parathyroidectomy, hippocampus, neuronal spike activity, excitatory and inhibitory responses

There is increasing evidence that estrogen and calcium ion are involved in learning and memory [29] and bilateral ovariectomy increases risk of cognitive impairment or dementia. The effect is age-dependent and suggests a critical age window for neuroprotection. [24]. The maintenance of Ca^{2+} homeostasis is a pivotal component of estrogen-mediated neuroprotection [4]. Estrogen is the main steroid hormone synthesized by and secreted from the ovary. Short-term estrogen exposure attenuates voltage-dependent Ca^{2+} current [14]. As estrogen is an important modulator in the actions of the vitamin D system, parathyroid hormone (PTH), and extracellular Ca, it is not clear whether estrogen is a direct regulator of vitamin D metabolism in vivo [2, 36]. It is now clear that estrogens exert rapid (also termed 'non-genomic' or 'membrane initiated') effects on many neurons located throughout the brain [18, 25]. The main factors which regulate PTH production are calcium, phosphate, vitamin D, and estrogens [11]. Parathyroidectomy (PTX) not only improves physical symptoms of hyperparathyroidism, but can also positively influence the patients' cognitive performance. These findings reflect the clinical observation of the patients' improved mental capacity after PTX [22]. The results point to the deranged functioning of dopamine and noradrenaline brain systems as a result of disorders in calcium homeostasis [28]. Age-related dysregulation of calcium dynamics in neurons is prevented by estrogen and its chronic replacement effects on Ca^{2+} current activity in hippocampal neurons of young and aged ovariectomized (OVX) rats [5]. Similarly, in OVX rodents, estrogen has also been shown to have signiûcant beneûcial effects on learning and memory. In addition, decreased estrogen levels in such animals are also accompanied by morphological, neurochemical, and molecular deûcits such as structural alterations in hippocampal dendritic spines [9]. Effects of estrogen on dendritic density were also seen in the prefrontal cortex, a brain region known to have a role in cognition. Ovarian hormones affect the density of 5-HT serotonin receptors [18] and, therefore, have an effect on emotional and cognitive behavior. Previous studies have shown an in-

creased dendritic spine density in hippocampal CA1 pyramidal cells after estrogen treatment of OVX rats and of hippocampal cell cultures [15]. In addition, it has been reported that estrogen potentiates presynaptic function in cultured hippocampal neurons [35] and enhances glutamate receptor-mediated excitatory postsynaptic potential [7]. Although primarily regarded as the female sex hormone, estradiol acts beyond the scope of the reproductive axis at various sites, including bone, liver, kidney, brain, heart, and vasculature. Additionally, estrogen replacement also lessens the risk and/or delays the onset of neurodegenerative conditions such as Alzheimer's disease [3], and provides cognitive benefits [26] in post-menopausal women. There is evidence that the number of muscarinic acetylcholine receptors is increased in the hippocampus of OVX rats, and that this increase is abolished by estradiol treatment [17]. Estrogen increases choline acetyltransferase activity in the basal forebrains and hippocampi of OVX rats [12]. Studies have proposed that the non-genomic effects by estrogen may stimulate mitogen-activated protein kinase [23] and extracellular regulated kinase signaling or intracellular Ca^{2+} release [20], due to specific plasma membrane estrogen. Properly controlled homeostasis of calcium signaling not only supports normal brain physiology but also maintains neuronal integrity and long-term cell survival [16].

The aim of present work was to examine the role of Ca^{2+}-dependent signaling events in hippocampal synaptic transmission, plasticity, and cell survival in condition of estrogen and parathyroid hormone deprivation caused by OVX and PTX. Electrophysiological studies by extracellular recording of hippocampal single-neuronal spike activity under high-frequency stimulation (HFS) of entorhinal cortex (EC) were performed on Albino rats after 6 weeks of OVX and 3, 6 days of PTX.

Material and Methods

The study was performed on 11 Albino rats (250±20). Under Nembutal anesthesia (40 mg/kg, i/p) we performed removal of ovary and parathyroid glands (OVX and PTX). In microelectrophysiological investigations after 6 week of OVX and 3, 6 days of PTX were performed extracellular registration of background and induced spike activity of single neurons of hippocampus under HFS of ipsilateral EC. In acute experiment the animals were immobilized with 1 % ditiline (25mg/kg i/p) and were given artificial breathing. The model of isolated rat brain had been received by transection of spinal cord (T_2_T_3) under local Novocain anesthesia. The stimulatory electrode was input in EC according to stereotaxic coordinates (AP -9, L ±3.5, DV +4.0 mm) and a glass recording electrode with 1 mkm diameter of tip was repeatedly submerged into hippocampus according to coordinates AP -3.5, L ±1.5-3.5, DV +3.0 – 4.5 mm. HFS (100 Hz during 1 second) was performed by means of rectangle charge by 0.05 ms duration and 0.16 mA amplitude. On-line registration and mathematical analysis of spiking activity were carried out on the basis of the program (worked up by V.S Kamenetski), which provides selection of spikes and exclusion of artefacts during HFS by amplitude dis-

crimination, which allows to evaluate not only tetanic, but also posttetanic activity. On the base of analyisis of peristimul spiking there were built the timing, frequency and cumulative histograms for single neurons, as well as a diagram of mean frequency. For statistic evaluation we used t-criteria of Student's test, the reliability of differences of interspike intervals before and after HFS, as well as non-parametric method of checking by using as a criteria the biselected test of Vilkokson-Mann-Whitney (VMW). After calculating of values of Student's t-statistics, z-statistics of VMW and comparing them with tabulated values of normal distribution (the levels of meanings are 0.05, 0.01 and 0.001), for analysis there was used the spiking of neuronal activity by statistic significant level ($P \leq 0.05$).

Results and Discussion

Neuronal Ca^{2+} homeostasis and Ca^{2+} signaling regulate multiple neuronal functions, including synaptic transmission, plasticity, and cell survival. Therefore disturbances in Ca^{2+} homeostasis can affect the well-being of the neuron in different ways and to various degrees.

In hippocampal neurons the variability of poststimulus excitatory and inhibitory responses caused by EC HFS using programmed multilevel mathematical analysis were performed. In intact rats the type of excitatory and inhibitory strict reproduced responses are as follows: tetanic potentiation (TP) in combination with posttetanic potentiation (PTP) (TP+PTP 17.4 %), tetanic depression (TD) in combination with posttetanic depression (PTD) (TD+PTD 42.2 %) and TD with PTP (TD+PTP 40.4 %). After 6 weeks of OVX dominated areactivity in neurons of CA1 and CA3 fields of hippocampus (45.5 %) in response to HFS EC. The other neurons were characterized by low repeatability and excitability: TD+PTD – 32.86 %, PTP -13.98 %, TD+PTP – 7.69 %, TP – 0 %. Figure 1 illustrates the registered spiking activity's peri event time histogram of sum spike and mean frequency in hippocampal neurons of OVX animals' group. The responses of HFS are classified corresponding to expression-areactive (Fig. 1 A), inhibitory (Fig. 1 B), excitatory (Fig. 1 C) and complex (TD + PTP) (Fig. 1 D). Mean frequency histograms' figure values (M_{BE}, M_{TT}, M_{BE}) of marked effects point out the decrease and increase of mean frequency's value during tetanic and posttetanic period. The highest values of background activity ($M_{BE} = 7.89$ spike/sec) in neurons showing inhibitory effects (Fig. 1 A) and the fewest ($M_{BE} = 2.90$ spike/sec) in neurons expressing excitatory effect were registered, which keep up a correspondence to normal criteria. The inhibitory responses are expressed slightly – 4.4 times (7.89 : 1.78 spike/sec) for the period of tetanisation and 1.4 (7.89 : 5.62 spike/sec) times in post tetanic period. The excitatory responses (Fig 1C) also were expressed slightly – 1.5 times (4.49 : 2.90 spike/sec) for the period of post tetanisation. Figure 1D represents TD+PTP responses of OVX group expressed by the following form – TD 5.7 times (5.82 : 1.02) decreased mean frequency and mean frequency of PTP – 1.3 times (7.46 : 5.82) in comparison with prestimulus value of mean frequency

(M_{BE}). It is distinctive that 45.4 % of neurons in CA1 and CA3 fields in OVX animals' group demonstrated areactivity, whereas in norm those neurons are absent. Our data suggest that OVX reduces hippocampal synaptic activity.

After 6 days of PTX, the 8.22 % of recorded neurons in CA1 field were areactive. In the multiplicity of combinations dominated (35.44 %) TD+PTP responses in CA3 field. In neurons of CA1 there were revealed TP which were combined not only with PTP (8.8 %), but also with PTD (4.5 %). In hippocampal dentate gyrus there were registered responses with deep inhibitory effects during the whole poststimulative period. The decrease of inhibition after 6 weeks of OVX is obvious, which can indicate to destruction of γ-aminobutyric acid (GABA).

We have performed a comparative analysis of expression of excitatory and inhibitory responses in PTX, OVX and norm groups. In Figure 2 (A, B) we have represented the PETH average histogram and peri event mean frequency values of every group. In hippocampal neurons of OVX group (Fig. 2 A) we registered the absence of TP and the fewest frequency in pre- and post stimulus period. The highest value of mean frequency of excitatory responses was recorded in norm during HFS (M_{TT}=32.45 spk/sec on Fig. 2 A – norm group). The identicaly expressed inhibitory responses (Fig. 2 B) dominated over the excitatory ones in three compared groups.

Thus there is impaired functional integrity caused by OVX and PTX and involvement of GABAergic neurotransmitter system in this neuropathology. The alterations of inhibitory circuitry exemplify the dynamic plasticity intrinsic to the brain even during neurodegenerative disease progression. The results allow us to suggest that the structures connected with brain memory (hippocamp, entorhinal cortex) are impaired by different mechanisms following OVX and PTX. It is known that estrogen regulates the GABAergic tone in the adult hippocampus [21]. However, the complex estrogenic effect on the GABAergic system is still unclear. In adult central nervous system neurons, GABA can induce both inhibitory and excitatory actions, which are predominantly controlled by the cation-chloride cotransporters. These findings suggest that basal levels of estrogen might contribute to a balance between the excitatory and inhibitory synaptic transmission onto CA1 pyramidal cells by regulating perisomatic γ-aminodecarboxilasa's and cation-chloride cotransporters' expression in the adult hippocampus [21]. Apart from these, Mendez P. et al. discuss the molecular mechanisms involved in the interaction of estrogen receptors and insulin-like growth factor-I receptors in the brain and their potential implications for neuroprotection [19]. There are similarities between actions of estrogen and BDNF in the hippocampus [30].

Ca^{2+} homeostasis undergoes subtle dysregulation in the physiological ageing [34]. Estrogen also has a physiological role in the regulation of intestinal calcium absorption and its deficiency in postmenopausal osteoporosis and following therapeutic oophorectomy may result directly in calcium malabsorption that is believed to be an important factor in the bone loss that occurs in these conditions [1].

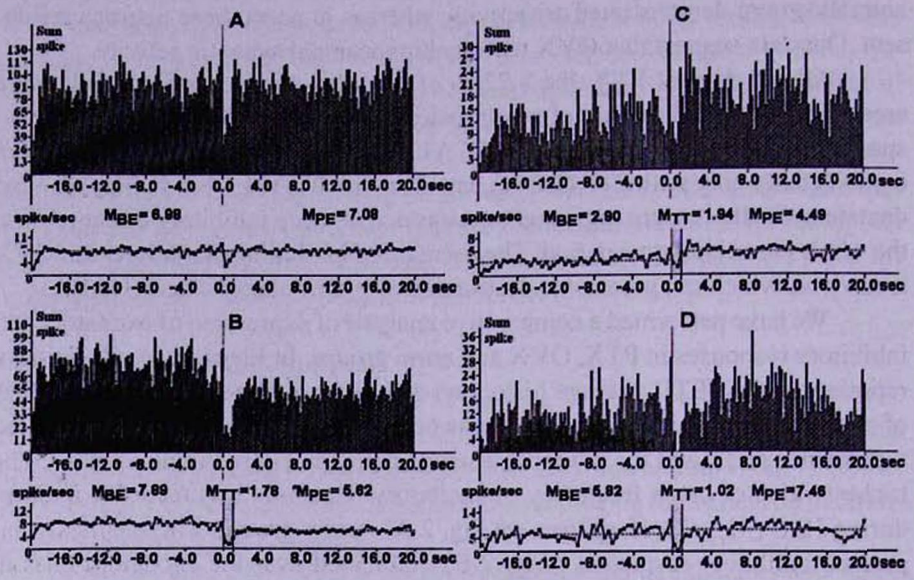

Fig. 1. A-D – peristimule histograms of sum spikes for areactive (A), TD+PTD (B), PTP (C) and TD+PTP (D) effects of hippocampal neurons under high-frequency stimulation (HFS) of entorhinal cortex at 6 weeks after bilateral ovariectomy; in the bottom (A-D) – diagrams of mean frequency of spike activity in real time, indicating average digital values of 20 sec before (MBE) and 20 sec after (MPE) stimulation and during 1 sec tetanic stimulation (MTT).

Hereinafter: BE (before event) – time interval before stimulation, PE (post event) – time after the stimulation, TT (time tetanization) – time of HFS; ordinate – sum of spikes in the time sequence, indicated endwise abscissa.

Age-related dysregulation of calcium dynamics in neurons is prevented by estrogen . The maintenance of Ca^{2+} homeostasis is a pivotal component of estrogen-mediated neuroprotection [4]. Activation of estrogen receptors and induction of intracellular Ca^{2+} influx via the L-type channels appear to be more closely associated with estrogen promotion of memory mechanisms [37]. L-type voltage-gated Ca^{2+}channels play an important role in dendritic development, neuronal survival, and synaptic plasticity. The recent studies have demonstrated that the gonadal steroid estrogen rapidly induces Ca^{2+} influx in hippocampal neurons, which is required for neuroprotection and long term potentiation. The mechanism by which estrogen rapidly induces this Ca^{2+} influx is not clearly understood [27].

The finding that estrogen interacted with the cholinergic system to influence attentional performance supports findings from the primary literature [33], showing that estrogen affects cholinergic functioning and attentional processing. A number of studies have investigated the interaction of estrogen and the cholinergic system and its effects on memory performance [8].

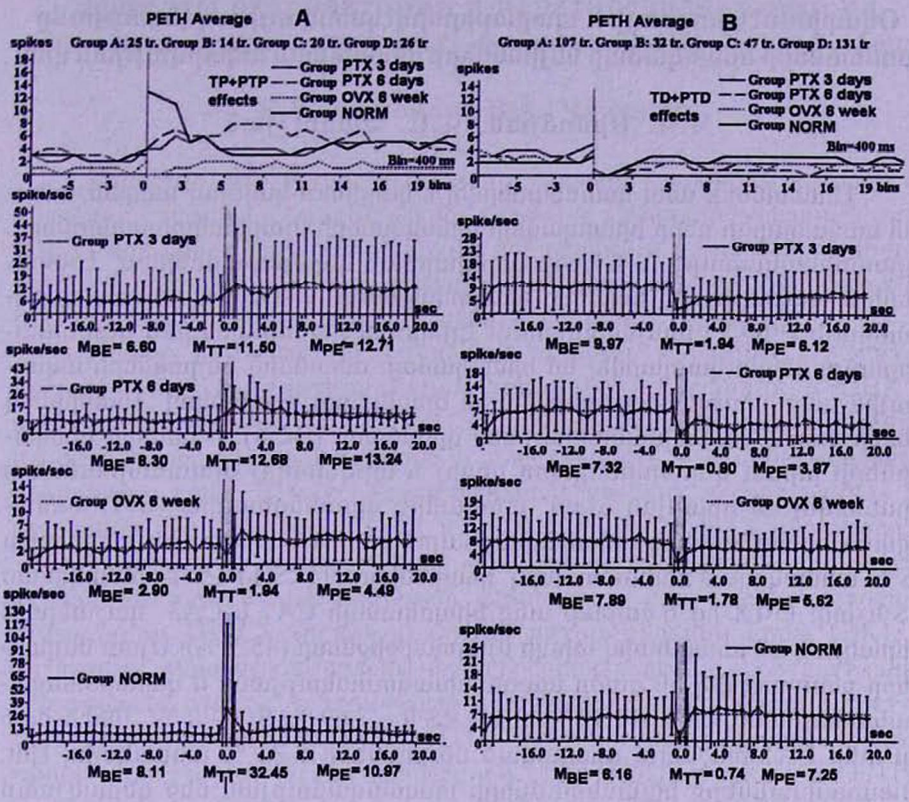

Fig. 2. PETH Average – complex averaged peristimule histograms of hippocampal neurons spiking in group of intact rats (norm) and of those after parathyroidectomy (PTX 3days and 6 days) and 6 weeks after bilateral ovariectomy (OVX 6 weeks) for excitatory (A) and inhibitory (B) effects at HFS of EC. Next to each group the number of tests is given. In the bottom (A, B) – diagrams of mean frequency of spike activity in real time, indicating average digital values of 20 sec before (MBE) and 20 sec after (MPE) stimulation and during 1 sec tetanic stimulation (MTT) for each group.

There is increasing evidence that estrogen and calcium ions are involved in learning and memory and bilateral OVX (as models for studying the effects of ovarian hormone deficiency) increases risk of cognitive impairment or dementia. Our data suggest that estrogen can regulate hippocampal synaptic plasticity and improve hippocampus-dependent cognition [10].

Furthermore, acute application of estrogens to hippocampal slices increases NMDA and AMPA receptor transmission [31], induces long-term potentiation and long-term depression [13], and rapidly modulates neuronal excitability in rat hippocampus [32].

Поступила 27.12.10

Օվարիումէկտոմիայի և պարաթիրոիդէկտոմիայի ազդեցությունը առնետների հիպոկամպի նեյրոնների սինապտիկ ակտիվության վրա

Կ.Վ. Սիմոնյան, Վ.Ա. Չավուշյան

Առնետների մոտ ոսումնասիրվել է կալցիում-կախյալ ազդանշանային համակարգի դերը հիպոկամպի սինապսների նյարդափոխադրիչների, պլաստիկականության և բջջի վերապրման գործընթացներում՝ էստրոգենի և պարաթիրոիդ հորմոնի դեպրիվացիայի՝ ՕՎՀ և պարաթիրոիդէկտոմիայի (ՊԹՀ) պայմաններում: Էլեկտրաֆիզիոլոգիական ուսումնասիրությունները կատարվել են հիպոկամպի առանձին նեյրոնների սպայկային ակտիվության արտաբջջային գրանցման եղանակով՝ էնտորինալ կեղևի բարձր հաճախականությամբ գրգռմամբ (ԲՀԳ): Ինտակտ կենդանիների խիստ վերարտադրվող դրդիչ և արգելակիչ պատասխանները դրսևորվել են հետևյալ ձևով՝ տետանիկ պոտենցիացիա (ՏՊ) համակցված հետտետանիկ պոտենցիացիայով (ՀՏՊ) և տետանիկ դեպրեսիա (ՏԴ) համակցված հետտետանիկ դեպրեսիայով (ՀՏԴ) և ՏԴ համակցված ՀՏՊ-յով: ՕՎՀ-ից 6 շաբաթ անց հիպոկամպի CA1 և CA3 դաշտերում գերակշռել են առեակտիվ տիպի նյարդաբջիջները (45.5 %): Մյուս նեյրոնները բնութագրվել են ցածր պատասխանունակությամբ և վերարտադրողականությամբ, ՀՏՊ -13.98 %, ՏԴ + ՀՏՊ – 7.69 %, ՏՊ – 0 %: ՊԹՀ-ից 6 օր անց CA1 դաշտում գրանցված նեյրոնների 8.22 % առեակտիվ էին: Պատասխանների համակցումների բազմազանության մեջ գերակշռում են CA3 դաշտի ՏԴ + ՀՏՊ պատասխանները: CA1 դաշտի նեյրոններում գրանցվել են ՏՊ՝ համակցված ինչպես ՀՏՊ-ով այնպես էլ ՀՏԴ-ով: Հիպոկամպի ատամնավոր գալարում գրանցվել են խոր արտահայտված արգելակող պատասխաններ ամբողջ հետստիմուլային ժամանակահատվածում:

Այսպիսով, ԳԱԿԹ-էրգիկ նյարդափոխադրիչ համակարգը ներգրավված է ուղեղի ֆունկցիոնալ ինտեգրացիայի խանգարման մեջ՝ առաջացված ՕՎՀ և ՊԹՀ հետևանքով: Ուղեղին բնորոշ արգելակիչ շղթաների փոփոխությունները հանդիսանում են դինամիկ պլաստիկականության օրինակ, նույնիսկ նյարդադեգեներատիվ հիվանդությունների զարգացման ընթացքում:

Արդյունքները թույլ են տալիս ենթադրել, որ հիշողության հետ կապված ուղեղի կառույցները (հիպոկամպ, էնտորինալ կեղև և այլն) էստրոգենի և պարաթիրեոիդ հորմոնի դեպրիվացիայի հետևանքով ախտահարվում են տարբեր մեխանիզմներով:

Эффекты овариэктомии и паратиреоидэктомии на синаптическую активность нейронов гиппокампа крыс

К.В. Симонян, В.А. Чавушян

Известно, что эстрогены и ионы кальция вовлечены в процессы обучения и памяти и билатеральное удаление яичников – овариэктомия (ОВХ) повышает риск когнитивных нарушений и деменций. С другой стороны, эстрогены и ионы кальция выступают в качестве факторов, регулирующих продуцирование паратиреоидного гормона.

Целью данного исследования явилось изучение эффектов эстрогеновой и паратиреоидной депривации, вызванной ОВХ и паратиреоидэктомией (ПТХ) на Ca^{2+}-зависимые процессы, а именно, на синаптическую трансмиссию и пластичность в гиппокампальных нейронах у крыс. В микроэлектрофизиологических исследованиях по истечении 6 недель после ОВХ и 3, 6 дней после ПТХ производили экстраклеточную регистрацию фоновой и вызванной спайковой активности одиночных нейронов гиппокампа при высокочастотной стимуляции (ВЧС) ипсилатеральной энторинальной коры (ЭК). У интактных животных выявлены четко воспроизводимые возбудительные и тормозные ответы: тетаническая потенциация в сочетании с посттетанической потенциацией (ТП+ПТП), тетаническая депрессия в сочетании с посттетанической депрессией (ТД+ПТД), а также ТД+ПТП. Спустя 6 недель в группе животных ОВХ в поле CA1 и CA3 гиппокампа доминировали ареактивные нейроны. Ответоспособные нейроны данной группы на ВЧС ЭК характеризовались низкой возбудимостью и воспроизводимостью ответов: ТД+ПТД – 32.86 %, ПТП – 13.98 %, ТД+ПТП – 7.69 %, ТП – 0 % . Спустя 6 дней в группе животных ПТХ в поле CA1 гиппокампа ареактивность проявляли 8.22 % зарегистрированных нейронов. В разнообразии комбинаций возбудительных и тормозных ответов доминировали ТД+ПТП ответы в нейронах поля CA3. В нейронах поля CA1 зарегистрированы ТП ответы, сочетанные как с ПТП, так и с ПТД. В данной группе в нейронах зубчатой извилины на ВЧС ЭК выявлялись выраженные на весь постстимульный период тормозные ответы.

Таким образом, ГАМКергическая нейротрансмиттерная система вовлечена в нарушение функциональной интеграции вследствие ОВХ и ПТХ. Альтерации ингибиторных цепей выступают в качестве образцов динамической пластичности, присущих мозгу даже в условиях прогрессирования нейродегенеративной патологии. Результаты позволяют предположить различные механизмы патологических нарушений при депривации эстрогена и паратиреоидного гормона в структурах мозга, связанных с обучением и памятью (в частности, гиппокамп и ЭК).

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