Journal of Life Sciences & Biomedicine, vol. 2(75), No 1, p. 110-115 (2020)

The role of neurochemical systems of the brain in the regulation of the hippocampal theta-rhythm

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Accepted for publication: 03 April 2020

In chronic experiments on the rabbits it has been shown that electric destruction of the dorsal amygdalo-fugal pathway leads to complete and persistent blockade of hippocampal theta rhythm in contrast to the ventral amygdalo-fugal pathway. In intact animals, electro- and chemostimulations of various limbic structures of the brain (amygdala, hypothalamus, reticular formation, medial septum nucleus) lead to the formation of well pronounced theta rhythm in the hippocampus, but after destruction of the dorsal amygdalo-fugal pathway no theta-rhythm in this structure was observed. Restoration of hippocampal EEG took place under the intra-hippocampal application of carbocholine and strychnine. It is proposed that one of the necessary conditions for the regulation of excitability of hippocampal neurons is the integrity of the dorsal amygdalo-fugal pathway through which the regulatory influences of the amygdala on the hypothalamic neuro-secretory cells are realized.

Keywords: *Hippocampal theta-rhythm, dorsal and ventral amygdalo-fugal pathways, electrical and chemo-stimulation, destruction*

INTRODUCTION

For many years, one of the controversial issues in the electrophysiology is the study of the hippocampal theta rhythm. The medial septum nucleus, standing at the entrance to the hippocampus, demonstrates the importance of education (Kichigina, Kutyreva 2002; Kitchigina, 2006; Kitchigina, Popova, Sinelnikova, Malkov, Astasheva, Shubina, Aliev, 2013; Mysin, Kitchigina, Kazanovich, 2015). In addition to the data, indicating to the pacemaker role of the septum, there are works showing a definite role of stem-diencephalon structures in the mechanisms of formation of hippocampal theta rhythm: a great importance is given to the reticular formation (Steriade, 1996), hypothalamus (Smythe,1991), thalamus (Smythe, 1991), locus cereleus (Berridge, Espana, 2000) and nucleus raphe (Kitchigina, 2006).

Recently it has been shown that the medial septum nucleus receives phases of the already encoded information from the uplink system, whose frequency determines frequency of the discharges of the septal hippocampal theta rhythm. There is evidence that this information comes from the supra-mammillary nucleus of the hypothalamus (Vertes, 1992).

Our earlier researches has shown that destruction of the dorsal amigdalo-fugal pathway (DAP), in contrast to destruction of the ventral amygdalo-fugal pathway (VAP), results in complete and irreversible blockade of hippocampal theta rhythm (Gasanov, Kasimov, Bagirova,1989). To clarify the reasons for the profound changes we have conducted electric and chemo-stimulation of the limbic structures of the brain (amygdala, hypothalamus, reticular formation, medial nucleus of the septum, hippocampus) before and after destruction of the DAP.

METHODS

Experiments were carried out on 16 mature rabbits having body mass 2.5-3.0 kg. Both recording the electrical activities from the hippocampus and septum and collection of the samples for morphological studies were performed 18-27 days later from such destruction. The EHipG was recorded from the dorsal hippocampus (the CA1field:

doi.org/10.29228/jlsb.48

P 3.0, L 2.0, H 18.0, and the CA3 field: P 0 2.0, L6.0, H17.0) and from the medial nucleus of the septum (A-3.0; L0.5; H10.5) on the encephalograph Medikor EEG-16E with the use of needle electrodes electrically insulated except for the tip. Spectral EHipG analysis was performed using standard electro-encephalographic approaches. Test substances were strychnine (1%), carbachol (0.5–1.5 μg), serotonin (5-50 μg), and noradrenaline (15-20 μg), applied in a volume of 5-6μL via a chemotrode, implanted into the field CA3. Electrocoagulation of the dorsal amygdalo-fugal pathway (stria terminalis) was performed using electrodes implanted in the pre-commissural area (A-1, L5, H18) with currents of up to 1.0 mA for 15–25 sec. Electrical stimulation of the extra-hippocampal structures (reticular formation: P9, L2.5, H18.2; basolateral nucleus of the amygdala: A-1, L5, H18; central nucleus of the amygdala: A-1,L5, H16; supraoptic nucleus of the hypothalamus: A-3, L2.2, H15.8; ventro-medial nucleus of the hypothalamus: AP0,L0.5, H17; medial mammillary nucleus of the hypothalamus: P2, L0.5, H18.5) and field CA3 was performed using an ÉSU-1 stimulator with square-wave impulses at frequencies of 5–100 per sec, amplitude 2–4 V, and duration 0.15 msec, for 15–30 sec; a histogram method was used for amplitude-frequency analysis of the EEG, as described Fujimori (Fujimoriet al., 1958).

RESULTS AND DISCUSSION

The results of the experiments showed that the baseline hippocampal and septal EEGs demonstrate irregular activity dominated by oscillations the range of 4–6 Hz. Comparison of the electrical activity of the hippocampus and different fragments of the conditioned reactions supports the existence of a marked correlation of the theta rhythm with such forms of behaviors as resting, voluntary locomotion, jumps and runs, and licking, being in agreement with the results obtained in our previous studies (Gasanov, Kasimov, Bagirova,1989). Application of the test substances to the dorsal hippocampus before lesioning of the stria terminalis led to ambiguous results. In particular, the effects of biogenic monoamines ultimately led to a redistribution of the peak of the EEG amplitude frequency characteristic in the hippocampus. In particular, while serotonin increased the EEG in the region 5–6 Hz, noradrenaline displaced the peak of the frequency characteristic to the region 4–5 Hz. The effects of strychnine and carbachol were significantly different. In this experimental situation, the application of carbachol (like strychnine) resulted in a generation of high-amplitude, regular theta waves of frequency 6–7.5 Hz at different time points, which with time course could transform into epi-discharges (Fig. 1, III, IV and V). The EEG changes seen after the applications of carbachol and strychnine started in all outputs simultaneously and were seen for prolonged periods of time (the maximum observation period was 3 h).

The destruction of the dorsal amygdalo-fugal way unlike to the destruction of ventral amygdalo-fugal way leads to a complete and irreversible blockade of hippocampal theta rhythm (Fig. 2, II and III). Dynamic observations of the EEG after unilateral lesioning of the stria terminalis showed that the onset of EEG depression often started before the transition period, which showed transient epileptiform activity which subsequently disappeared, leaving only super slow oscillations. On this background we were unable to record neuron spike activity from the field CA3 of the hippocampus, though continuing recording resulted in the appearance of occasional neuron action potentials in the cerebral cortex. Administration of biogenic monoamines into the hippocampus after lesioning of the stria terminalis did not induce any changes at all. The electrical stimulations of the various extra-hippocampal structures (mRF, hypothalamus, amygdala) did not bring to recovery of the electrical activity of the hippocampus, while stimulation of the hippocampus itself produced only epi-discharges, when the maximal stimulating electric current was used. The effects of the applications of carbachol and strychnine were rather different. In this situation, there was a tendency to recovery of the overall activities of the hippocampus and septum, with some features consisting of short-lived (20–30 sec) periodically repeated generation of regular rhythmic activities in the range 0.6-7.5 Hz. Attention is drawn to the fact that, on one hand, recovery of the electrical activities in the hippocampus and septum occurred spontaneously in all outputs, while, on the other hand, there was a marked synchronicity in the generation of the electrical activities.

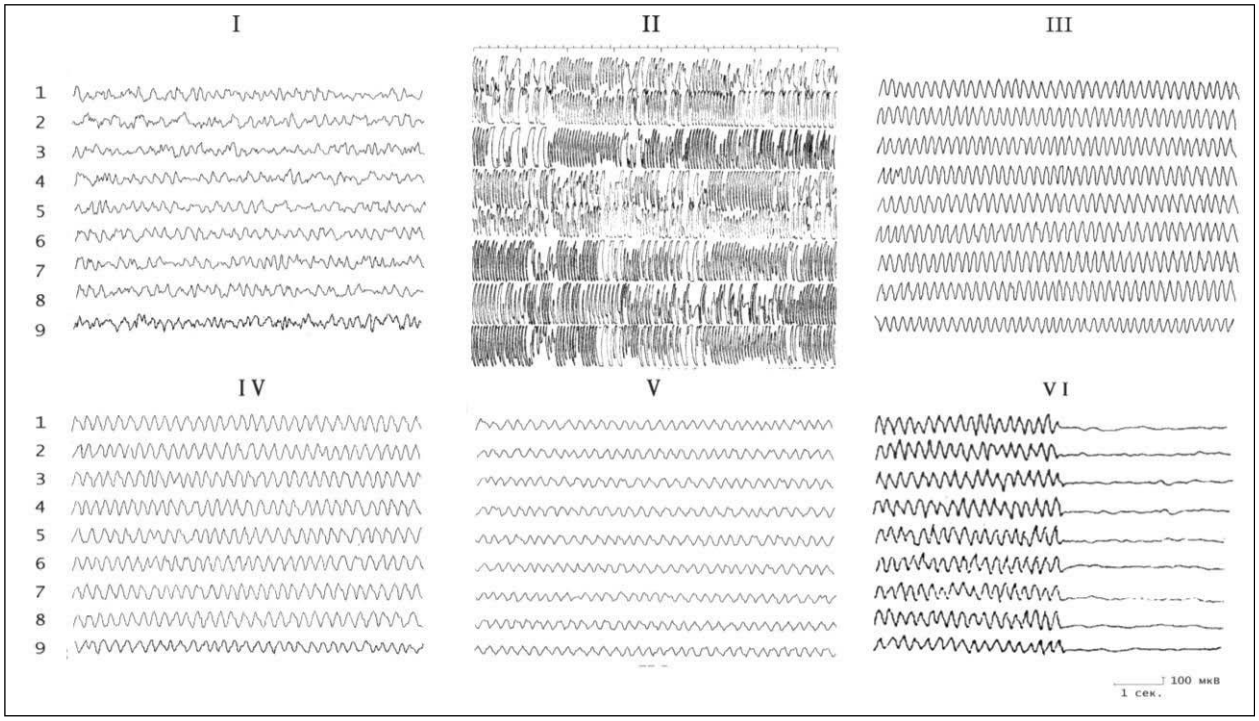

Figure 1. The influences of electric and chemical stimulations of the field CA3 of the dorsal hippocampus on the electrical activity of the hippocampus. I - baseline; II - instant electrical stimulation; III-after application of carbachol; IV-after application of serotonin; V - after application of noradrenaline; VI - application of carbachol on the background of the destruction of the dorsal amigdalo-fugal way.1,2-field CA1; 3,4-field CA3 of the ipsi- and contralateral hemispheres; 5,6 - ventral hippocampus of the ipsi- and contralateral hemispheres; 7,8 - dentate gyrus of the ipsi- and contralateral hemispheres; 9 - medial nucleus of the septum.

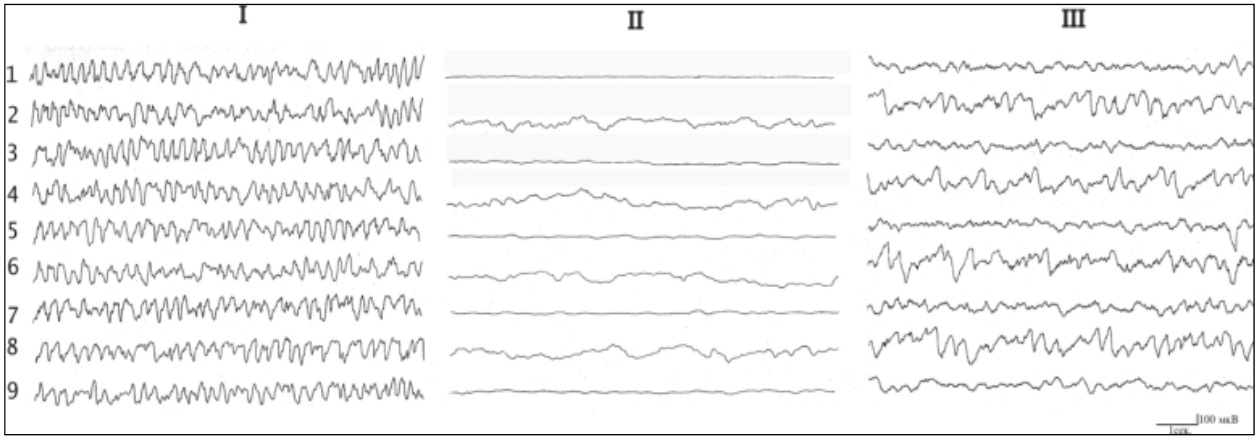

Figure 2. Changes in hippocampal electrical activity on the rabbits under destruction of the dorsal and ventral amigdalo-fugal ways. I-baseline; II-after destruction of the dorsal amigdalo-fugal way; III-after destruction of the ventral amigdalo-fugal way. The rest designations are the same as on Figure 1.

The effects of carbachol and strychnine were mostly similar and were long-lasting. In addition, analysis of the behavioral reactions provided evidence that conditioned responses persisted under the lesioning of the stria terminalis, with only one element to increase - is the latency of the response to the conditioned signal (2.0–2.5 sec as compared to 1.0–1.5 sec before lesioning). Hence, the analysis of our data allows to make a conclusion that the actions of various neurochemicals in the EEG activities of the hippocampus have a number of common and distinct properties. The former includes: 1) the occurrence of synchronized theta wave activity; 2) the absence in the different areas of the hippocampus of differentiation of the bioelectric reactions; 3) disturbances of the regularity of the theta-wave activity and the emergence of epi-discharges by increasing the doses of the studies monoamines injected into the brain structures. As for the properties that distinguished the actions of the applied neurochemical agents, they include: 1) the emergence of dominant frequency of 6-7.5 numbers/sec for the cholinergic, 5-6 numbers/sec – for the serotonergic and 4-5 numbers/sec for the noradrenergic stimulations of the nuclei of the amygdala, hypothalamus, midbrain reticular formation, and the medial nuclei of the septum and hippocampus; 2) changes in the amplitudes of the oscillations of synchronized potential compared to the baseline EEG activity, which reached its peak on the background of administration of cholinomimetics, average values under the administration of 5-HT and was below the baseline level under administration of NA. Considering the available data in the literature about the importance of studying brain structures in the regulation of the pituitary-adrenal cortex, one can assume that changes in the excitability of hippocampal neurons are caused by different electrical and neurochemical effects on the investigated structures of the limbic system. In regulation of the pituitary-adreno-cortical system a variety of neurotransmitters (acetylcholine, NA, 5-HT, dopamine, GABA, prostaglandins, etc.) can participate in (Sapronov, 1998).

The data available in the literature indicate that under the influence of large amounts of corticosteroids in the blood, in the hippocampus rhythmic activity with a frequency of 4-6 numbers/sec is recorded, and under the local application of cortisone or hydrocortisone into the hippocampus, the excitability level of the hippocampal pyramidal cells significantly increases and it forms convulsive activity, which, according to the authors, is the evidence of the direct action of corticosteroids on the dendrites of the hippocampal pyramids (Lishshak, Endreci, 1967; Endroczi, 1972). The results suggest that the regulation of hippocampal theta rhythm, as well as the functional activity of the hypothalamic-pituitary system, bears poly-mediatory character and is not determined strictly by a single brain monoaminergic mechanism, ensuring the reliability of the pituitary-adrenal response to these pressures, which is very important in maintaining the homeostasis. All these, obviously, present the huge compensatory potential of the CNS. A complete and irreversible blockade of the hippocampal EEG, induced by destruction of DAP, clearly indicates that under the given conditions the hypothalamic-pituitary system is posed at low level-violation formation rate of secretion of ACTH and corticosteroids. So, the results of the study indicate to the modulating effects of the limbic brain structures on the hippocampal theta rhythm and obviously on the hypothalamic-pituitary system, as well as the activating role of the amygdale in the activity of the hypothalamic neurons. All above said indicate that a prerequisite for the regulation of excitability of the hippocampal neurons is the integrity of the amygdalo-hypothalamic connections, through which the regulatory effect on the activity of the amygdalo-hypothalamic neurosecretory cells is realized.

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Hippokampal teta ritminin tənzimlənməsində beyin neyrokimyəvi sistemlərinin rolu

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Dovşan üzərində aparılan xroniki təcrübələrdə, dorsal amigdalofugal yolun elektrolitik zədələnməsi, ventraldan fərqli olaraq, hipokampal teta ritminin tam və dönməz blokadasına səbəb olduğu göstərilmişdir. Hippokampda teta ritminin formalaşmasında səbəb olan amigdala, hipotalamus, retikulyar formalasiyasının müxtəlif nüvələrinin və septumun medial nüvəsinin elektrik və kimyəvi qıcıqlanması dorsal amigdalofugal yolun məhv olması şəraitində onlara xas olan xüsusiyyətlərini nümayiş etdirmədi. Hippokampda EEG-nin bərpası yalnız karbokolin və strixninin intrahippokampal enjeksiyası ilə müşahidə edildi. Güman olunur ki, hippokampal neyronların həyəcanlılığının tənzimlənməsinin şərtlərindən biri də amigdala hipotalamik neyrosekretor hüceyrələrin fəaliyyətinə tənzimləyici təsir göstərdiyi dorsal amigdalofugal yolun bütövlüyüdür.

Açar sözlər: *Hipokampal teta ritmi, dorsal və ventral amigdalofugal yollar, elektro-, xemostimulyasiya, dağılma*

Роль нейрохимических систем мозга в регуляции гиппокампального тета-ритма

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В проведенных на кроликах хронических экспериментах было показано, что электролитическое повреждение дорсального амигдалофугального пути, в отличие от вентрального, приводит к полной и необратимой блокаде гиппокампального тета-ритма. Электро- и хемостимуляция различных ядер амигдалы, гипоталамуса, ретикулярной формации и медиального ядра септума, приводящие к возникновению тета-ритма в гиппокампе, не проявляли свойственного им характера разрушения в условиях дорсального амигдалофугального пути. Восстановление ЭЭГ в гиппокампе отмечалось только при внутригиппокампальном введении карбохолина и стрихнина. Предполагается, что одним из условий регуляции возбудимости нейронов гиппокампа является целостность дорсального амигдалофугального пути, посредством которого осуществляется регуляторное влияние амигдалы на деятельность гипоталамических нейросекреторных клеток.

Ключевые слова: *Гиппокампальный тета-ритм, дорсальный и вентральный амигдалофугальные пути, электро-, хемостимуляция, разрушение*