

## Some Aspects of Morphofunctional Organization of Germinal Regions of the Hippocampus and the Olfactory Bulb in Young and Old Mice

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**Abstract:** *The germinal area of a hippocampus and olfactory bulb is structured on a type of morphofunctional zones. Proliferation of cambial cells in each subunit of the zone happens not simultaneously: first the first 6 cells, and then the other 6 divide. The differentiation of daughter cells occurs in the electric field excited by 12 pairs of mother and daughter cells received during cambial cells division. The quantity of cambial cells in the olfactory bulbs and the hippocampus falls with aging. It is connected with decrease in a share of an inactive Src-kinase and RhoA in all the organism germ loci including a brain. At the same time formation of neurons cytoskeleton and their processes suffers, the spasm of cells increases and the proliferative activity of cambial cells falls. In a hippocampus decrease in the proliferative activity of cambial cells is expressed more than in olfactory bulbs due to the influence of glucocorticoids which strengthen a spasm of cells and by that continue to reduce cell proliferation.*

**Keywords:** *morphofunctional zone, hippocampus, olfactory bulb, regulation of cambial cells quantity, inactive Src-kinase*

### 1. INTRODUCTION

The structural organization of tissue is a basis for functional activity of cells. Now there are articles demonstrating that not single cells, but their communities or proliferative units function, in which the concrete regularities defining all the processes of cell life activity operate [4,11,19], In the center of each functional unit there is a cambial cell surrounded with its offspring. But the cells can be united not only in functional units, but larger structures in which processes of proliferation and a differentiation proceed.

Earlier we have offered the concept of the morphofunctional zones in which the principles of the

work of proliferative units, united in zones are stated [23]. Thus, the morphofunctional zone consists of two subunits with 12 cambial cells in each.. First, the cambial cells of the first subunit divide and then of the second. In each subunit not all 12 cambial cells proliferate simultaneously: first, the first 6 cells and then the other 6. As a result of 12 cambial cells division, the electric field is excited in which the daughter cells are differentiated. Stroma promotes the differentiation, because it relaxes the cortex of epithelial cells, therefore they can be stretched and differentiated by force of electric field. .

Two key proteins take part in the processes of proliferation and differentiation in the morphofunctional zone: Src-kinase and RhoA. Proliferation of cells in the morphofunctional zone is absent if RhoA strongly prevails over Src-kinase or on the contrary if the Src-kinase considerably exceeds RhoA.

In literature there are data that not only peripheral organs tissues have a modular structure, but the brain tissue also. At the same time neurons are united in the vertical mini-columns containing 110 neurons [14, 15, 16]. Several vertical mini-columns can form larger structures processing information. The idea that mini-columns are formed due to the locus organization of the brain germ areas has been put forward for the first time by Rakic [15]. Consequently Reznikov and Nazarevskaya [18] have experimentally proved asynchrony in neurons production in mice neocortex and hippocampus and also have defined average number of the neurons which have turned out during one mitotic cycle.

It was interesting to study the organization and functioning of the germ loci of a hippocampus using the principle of the morphofunctional zones. The tissue of

the olfactory bulb was studied also for the comparison in different intensity of cells proliferation in these two structures of the brain and for revealing the possible reasons influencing this process.

## 2. MATERIAL AND METHODS

Experiments were performed on female BDF 1 mice weighing 20 g at the age of 2,5-3,5 months (n=10) and 1,9-2.5 years (n=5). We allocated hippocampi and olfactory bulbs, then made the average thickness prints of these tissues and fixed them in 10% neutral formalin. Because the hippocampus lasts along the internal wall of the underhorn of the lateral ventricle of a brain, prints included a part of the periventricular regions. Prints were stained with hematoxylin for a research of the morphofunctional state of cell population. Studying of cell population was carried out on a "MultiMeter" (Russia) video analyzer with use the method developed by us [23]. The series of cells were formed according to cells degree of ellipticity (DE), because this parameter very thinly and quickly reacts to changes in the functional state of the cells. Two thousand cells were analyzed in each sample.

We distinguished the narrow cells (DE 0,11-0,275) which are the earliest offspring of the cambial cells, therefore according to their quantity it is possible to observe a portion of cambial cells in the population. Then narrow cells transit into oval (DE 0,625-0,0,775), and the latter - into reserve cells which represent the depot on cell regeneration in population.

Reserve cells (DE 0,6) in the process of population regeneration pass into transitional (DE 0,45-0,575), and then into the elongated cells (DE 0,3-0,425) which directly enter into mitosis. As the result, the round cells (DE 0,8-1,0) which are gradually mature into final cells turn out.

For the identification of cells area change in age aspect we measured this parameter in pixels.

The other part of preparations was processed on identification of tyrosinase activity in cell population. For this purpose the prints were fixed in 10% neutral formalin within 20 minutes, then placed in incubatory solution (0,3% DOFA with addition of the phosphatic buffer) at 37° C for 3 hours. After that we stained nuclei with hematoxylin within 1 minute. The tyrosinase activity was revealed with the help of brown-black granules in the cells. We defined the quantity of cells with tyrosinase activity in 20 visual fields in cell

population of the hippocampus and the olfactory bulb (Ob.16, Oc. 10).

## 3. RESULTS AND DISCUSSION

Archeocortex and neocortex have the structural organization on type of modules which neurons are united in integrative units [14, 15, 16]. Emergence of these modules is connected with the proliferation of cells in germinal regions of a brain, then the neurons are gradually matured, and then migrate along the radial fibers and form the mini-columns. However in the germinal areas not single cells proliferate, but groups of cells which form proliferative units. Using a <sup>3</sup>H-thymidine injection, Reznikov and Nazarevskaya [18] have revealed that in one-day mice neocortex and hippocampus the neighboring groups of the germ cells enter into proliferation not simultaneously. Therefore within a day precursors of neurons in such sites perform two divisions. As a result, 6-9 cells are formed during one mitotic cycle, and two - 12-18 cell, which then enter into a neuronal differentiation.

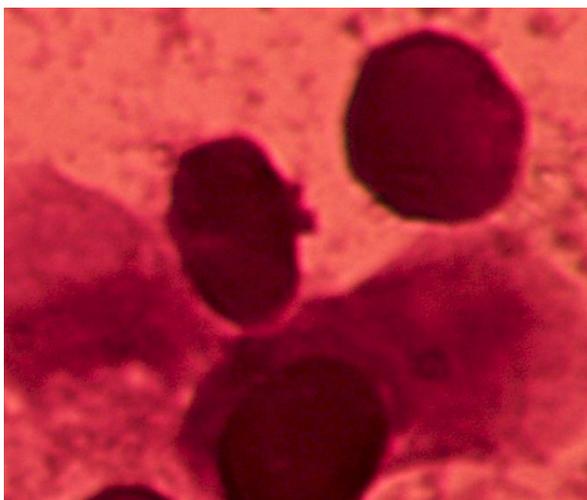
These data are well agreed with our results about the structure of epithelial and stromal tissue on type of the morphofunctional zones [23]. In brain tissue, as well as in these tissues not single cells, but groups of cells function. First of all 6-9 cambial cells enter into proliferation, and then the other 6 which then are exposed to a differentiation. Therefore, the germinal loci of the brain tissue have the features of epithelial and stromal morphofunctional zones.

It is known that in the postnatal period the mammalian cambial cells of an olfactory bulb situate in a subventricular region from which they migrate in this structure of a brain via the rostral migratory stream and proliferate with the subsequent differentiation [2,10, 13, 26]. In the hippocampus there is own source of the cells proliferative pool - it is a subgranular layer of the dentate gyrus. It is considered that in the embryonic period these cambial cells arrive here from a ventricular zone [17]. In the postnatal period replenishment of nervous cells population in an olfactory bulb and a hippocampus happens also due to cambial cells which are near vessels [7].

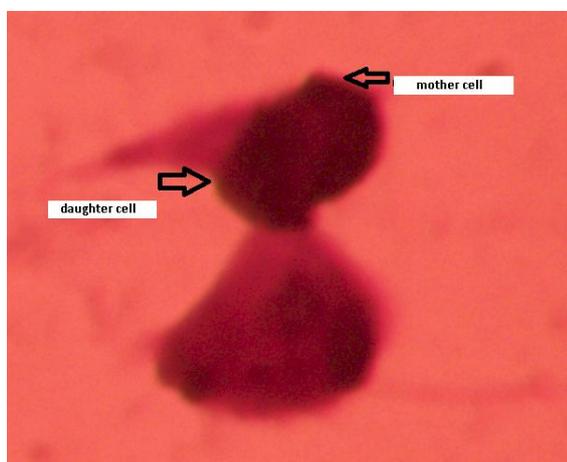
We revealed, that small, round cells, having dense cytoplasm were located . in the periventricular region and around vessels in the hippocampus and the olfactory bulb. These cells were found in general at young mice. Near vessels such cells were usually linked in groups with 3 cells in each. Then they began to

divide, crawling at each other because they had the division axis different from the other cells.

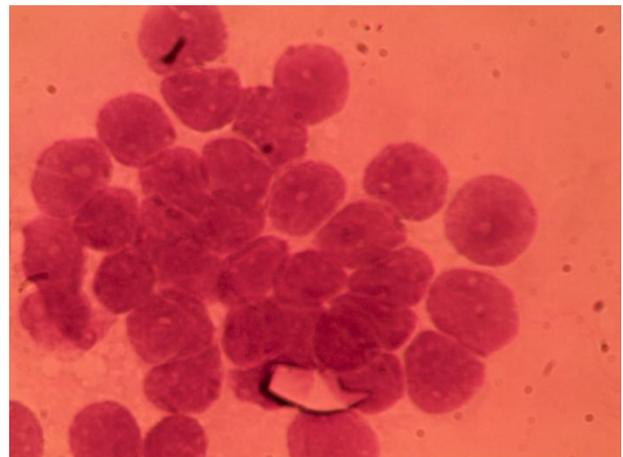
Therefore it becomes clear why 6 new cells are synchronously formed in the brain germinal loci, as well as in epithelial and stromal morphofunctional zones. Features of cambial cells division in the hippocampus and the olfactory bulb coincide completely with cambial cells of epithelial and stromal tissue (epidermis and a papillary dermis, eye cornea limb tissue, marrow). Two cells which turned out after the cambial cell division do not disperse for a long time. Then one of the cells – mother, acquires the canoe-like form, and another – daughter, is gradually drawn out and polarized (Fig. 1 and, b). Cells of the germinal areas create the rosettes-like structures similar to epithelial tissue. (Fig. 2).



**Fig 1(a):** Two cells which have turned out during the cambial cell division in the mouse hippocampus don't disperse and are connected with each other for a long time.



**Fig 1(b):** The mother cell gets a canoe-like form and is constricted, and daughter cell is polarized. Staining with hematoxylin, x1000.



**Fig 2:** In the germinal regions the cells form the rosettes-type structures. Staining with hematoxylin, x400.

Earlier, we found that the differentiation of the daughter cells in the epithelial morphofunctional zone occurs only when the number of mother and daughter cells pairs reaches 12 [23]. Thus, the summary electric field, necessary for daughter cells stretching is excited. Considering that brain germinal loci have the features inherent in morphofunctional zones and the differentiation of neurons occurs only after the quantity of new cells reaches 12-18, it is possible to assume the mechanism of neurons differentiation in the electric field, identical with epithelial tissue.

Interestingly, electric field controls the number of cambial cells and their stem characteristics. Really, the cambial cells having a vertical division axis, during proliferation give two equivalent undifferentiated cells lying one over another. The top cells at contact with a basal membrane will fill up a pool of cambial cells until the number of pairs reaches 12. After that the electric field is excited, which is necessary and sufficient for stretching of the top cells lying on the lower cells, that leads to formation of the daughter cells.

At the same time there is a harmonious work of cambial cells of the germinal regions and the stromal microenvironment which relaxes a cortex of cambial cells for the purpose of stretching them in the electric field. If the odd cambial cells in this group have undergone division, they will remain constricted in this case, that, apparently, will cause the pycnosis of these cells.

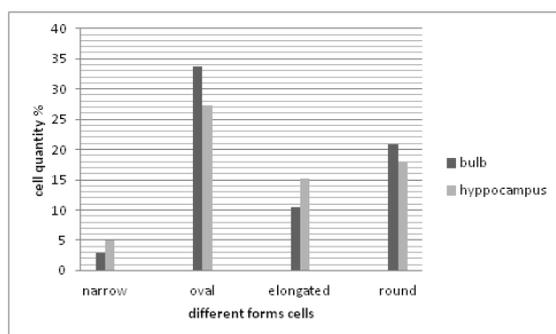
Interesting data were obtained by Lewis, Balaze and Korr [9, 12] who observed in the hippocampus and cerebellum a pycnosis degeneration of cells nuclei which had the mitotic origin.

Thus, cambial cells with a vertical division axis, without changing its direction, in one cases can fill up the population, and in the others – give the daughter cell which is exposed to a differentiation.

The study of the prints of hippocampus and olfactory bulb tissue by method of automated morphometry has revealed that in the tissue of these structures there are the same, as well as in the epithelium groups of cells: narrow, elongated, transitional, oval and round.

In the olfactory bulb of young mice at the age of 2,5-3,5 months the quantity of the narrow cells showing a portion of cambial cells is 2,9%. These cells gradually pass into oval (33,7%). Reserve cells transform into transitional (18,7%), and the latter - into elongated (10,5%) at which division round cells (20,9%) maturing to final cells turn out.

When we compared the histograms of cell distribution in the hippocampus and the bulb in group of young mice it was revealed that in the hippocampus the quantity of narrow cells increased up to 4,9% (in the bulb - 2,9%), the number of oval cells decreased to 27,2% (in the bulb - 33,7%) (Fig. 3). It demonstrates that in the hippocampus of young mice in comparison with their bulb the transition of narrow cells into oval occurs slower. Besides, the process of the elongated cells entering into mitosis is slowed, i.e. the quantity of the elongated cells increases in the hippocampus up to 15,2% (in the bulb - 10,5%), and round cells decreases to 17,9% (in the bulb - 20,9%).



**Fig 3:** The comparative quantitative characteristic of various cell forms in the bulb and the hippocampus of young mice. X axis – various forms cells in the bulb and the hippocampus, y axis – cells quantity in %.

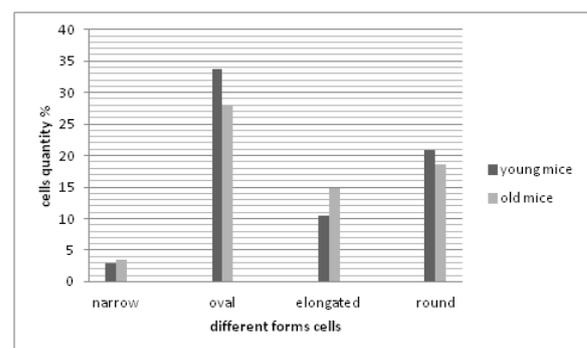
Thus, the processes of proliferation in the hippocampus of young mice proceed more slowly, than in the bulb of mice of the same age.

We also compared the histograms of cell distribution in the hippocampus and the olfactory bulb in the group of

old mice (1,9 - 2,5 years). It is revealed that in the hippocampus the quantity of narrow cells (2,9%) decreases in comparison with the bulb (3,5%), at the same time the share of oval cells which are the product of their conversion doesn't change in comparison with a bulb and reaches 28,1%.

Therefore, in the group of old mice some tendency of decrease in the cambial cells number in the hippocampus in comparison with the olfactory bulb is observed.

If to compare the histograms of cell distribution in the bulb of old and young mice, then the following has become clear. In the bulb tissue of old mice there is a decrease in proliferative activity of cells in comparison with young mice, because the narrow and elongated cells are slow to enter into proliferation. Thus, at young mice the number of narrow cells in the bulb was 2,9%, at old – 3,5%, the quantity of the oval cells which are the derivatives of narrow at young mice was 33,7%, at old – 28,1%. At the same time the total amount of narrow and oval cells in group of young mice consisted 36,6%, and at old – has decreased to 31,6%. The number of the elongated cells (14,8%) at old mice has increased in comparison with young mice (10,5%), because the entering of these cells into mitosis is delayed, therefore the quantity of round cells decreases to 18,6% (at young 20,9%) (Fig. 4)



**Fig 4:** Change of different forms cells number in the olfactory bulbs of young and old mice. X axis – various forms cells in a bulb of young and old mice, y axis – cells quantity in %.

Thus, in the bulb tissue of old mice in comparison with young mice there was a falling in cambial cells number and decrease in proliferative activity due to the delay of the cells entering into mitosis.

When we compared the histograms of cell distribution in the hippocampus of old and young mice the following was observed. The quantity of narrow cells decreases in old mice to 2,9% (in young mice - 4,9%),

and the number of their derivatives – oval cells fluctuates slightly of both groups, old and young mice – from 27,2 to 28,1%. Therefore, at old mice in comparison with young the decrease in quantity of narrow cells which indicate a share of cambial cells has happened not due to the strengthened transition of these cells into oval, but owing to decrease in their number.

Thus, the carried out research has shown that in both groups, young and old mice the proliferative activity of cells in the hippocampus is lower in comparison with the olfactory bulb. At young mice this decrease is caused by slower entering into mitosis of the hippocampus cells in comparison with a bulb. At old mice in comparison with young the falling of proliferative activity in the hippocampus and the olfactory bulb is connected with decrease in cambial cells number. Because in the hippocampus the decrease is more expressed, than in the bulb, it causes lower proliferative activity in the hippocampus of the old mice in comparison with the bulb of similar aged mice.

The proliferative activity of cells is closely connected with their tyrosinase activity. In our previous works it is shown that the earliest offspring of cambial cells have the tyrosinase activity [23, 24]. It usually is found in the cells having the raised expression of RhoA, i.e. the epithelial cells. In the fibroblasts the tyrosinase activity isn't expressed because the microenvironment of the fibroblast daughter cell plentifully activates in it the Src-kinase by means of the SH3 domain [22]. Therefore in the fibroblasts the quantity of the active Src-kinase in comparison with inactive increases. Interestingly, only the inactive Src-kinase can participate in formation of the cytoskeleton and melanogenesis [24]. Really, Src participates in microtubules assembly first of all as the protein joining tubulin dimmers. At a melanogenesis thiol groups of an inactive Src-kinase are necessary for reduction of copper cations without which the tyrosinase doesn't work

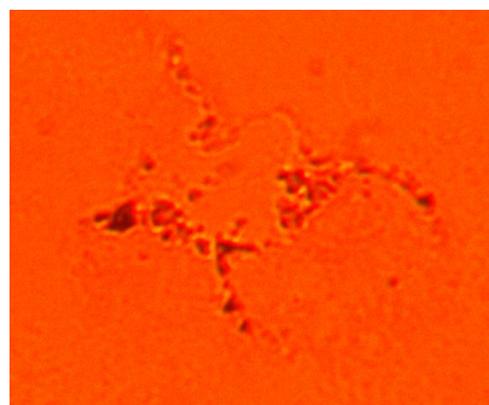
Thus, in fibroblasts the portion of the remained inactive Src-kinase will be used generally for the cytoskeleton formation..

In the epithelial cells the microenvironment produces the growth factors (such as EGF) which activate the Src-kinase much more weakly (by means of the SH2 domain) in comparison with fibroblasts growth factors [22]. Therefore in the epithelial cells the portion of the

active Src-kinase will decrease, and inactive - increase. Finally, the inactive Src-kinase due to the increase in its quantity will participate in both processes – formation of a cytoskeleton and melanogenesis. It causes emergence of a pigment in the epithelial cells..

In nervous cells the RhoA activity is higher, than in epithelial cells that is caused by an embryogenesis. It is known that nervous tissue is formed in an embryogenesis of an ectoderm under the influence of a chorda. The chorda has high activity of the Src-kinase and induces the expression of this protein in an ectoderm, so the latter then transforms into a neuroepithelium. The Src-kinase inactivates a part of the RhoA protein that promotes a softening of the cell cortex. Due to the development of the actin-myosin complex there are forces extending a cell along its main axis. It leads to emergence of mechanically intense cells which are extended and polarized in the vertical direction [3, 6]. But stretching of cells leads to emission of a new portion of an inactive Src-kinase which doesn't act on RhoA therefore in nervous cells along with a high expression of an inactive Src-kinase there is a high content of RhoA protein. As a result early offspring of cambial cells of nervous tissue have to obtain the tyrosinase activity.

We studied the tyrosinase activity of the hippocampus and. the olfactory bulb cells. Tyrosinase was revealed in early offspring of the daughter cells in which the processes were slightly planned, and in young neurons, and the cell processes were stained most intensively. In young mice the quantity of such cells in the hippocampus was 1-2 cells on 4 visual fields, and in the bulb - 1-2 on 2 visual fields (Fig. 5). At old mice the number of cells with tyrosinase activity in the bulb was 1 cell on 5 visual fields, and in the hippocampus – 1 cell on 10 visual fields.



**Fig 5:** In the bulb of the mouse at the age of 3,5 months two young neurons poses the tyrosinase activity. Histochemical DOPA-reaction, x1000.

Thus, the quantity of cells with tyrosinase activity in the hippocampus and the bulb decreased with age, and the number of such cells in the hippocampus is much lower, than in the bulb.

It is shown above that the cells with tyrosinase activity testify about a prevalence of an inactive Src-kinase portion over active and high RhoA in cell population. Decrease with aging in such cells number in the hippocampus and the olfactory bulb demonstrates that the share of the inactive Src-kinase participating in the process of a cytoskeleton formation and cell differentiation and also in the pigment production falls. But the structure of the axons, dendrites and cones of growth consists of the actin microfilaments and microtubules in which formation the inactive Src-kinase participates, therefore it will lead to shortening of processes and decrease in interrelation of neurons with aging.

Falling of an inactive Src-kinase part at old mice leads to a spasm of the cells that promotes decrease in proliferative activity of all the cells, including cambial cells of various tissues and organs. Decrease in quantity of an inactive form of this enzyme is connected with attenuation of hormonal activity and decrease in effect of estrogen on all organism tissues including a brain. Really, estrogens directly activate Src-kinase, therefore during the hyperestrogenemia period the quantity of the active Src increases and inactive – decreases. Then the hypoestrogenemia leads to reduction of a share of both an active, and inactive Src-kinase and also RhoA. Considering that RhoA during this period is inactivated to a lesser extent, than at a hyperestrogenemia, there will be a spasm of cells that will cause decrease of the cells area.

We have performed measurement of the cells area of the hippocampus and olfactory bulbs at young and old mice. Reduction of the cells area of the hippocampus (221,3 pix.) and olfactory bulb (212,9 pix.) is revealed at old mice in comparison with young mice. (263 pix. and 246 pix. respectively). The other authors also testify about the reduction of hippocampus pyramidal neurons areas with aging. [27].

The greatest decrease of cambial cell number in the hippocampus in comparison with the olfactory bulb is caused by the fact that the hippocampus is exposed to additional influence of glucocorticoids [8, 20].

We revealed earlier that the cell proliferation in the morphofunctional zone is defined by a ratio of two key

proteins – Src-kinases and RhoA because these proteins participate in formation of a cytoskeleton and the contraction apparatus of a cell [25]. Proliferation of cells occurs when RhoA expression more, than moderately exceeds a Src-kinase expression because Src inactivates a part of RhoA protein, and the remained its part will participate in a mitosis. If RhoA expression in cells is excessively raised, then it will cause a cell spasm and proliferation depression. At strong augmentation of the Src activity the proliferation of cells will also decrease as the Src-kinase inactivates RhoA. Because in nervous cells there is a high expression of RhoA, these cells can proliferate only at moderate depression of this protein expression. It is known that in a hippocampus there is a large number of receptors to glucocorticoids. The quantity of a corticosterone at mice and a hydrocortisone at people grows with aging that has neurotoxic effect. For example, decrease in the level of a corticosterone at old rats leads to strengthening of proliferative processes in a hippocampus [21].

Increase in the level of glucocorticoids with aging may be connected with the following. Thus, the brain cells have a high RhoA and inactive Src-kinase expression in young people. The hypothalamus sends an impulse with gradually increasing of RhoA expression to a pituitary

where synthesis of adrenocorticotrophic hormone (ACTH) begins. ACTH and melanocyte-stimulating hormone (MSH) are in the group of the peptides having the general origin therefore ACTH has also melanocyte-stimulating activity. At the same time the action of MSH is directed generally not to synthesis of a pigment, but to its dispersion that is reached by strengthening of an active Src-kinase portion and decrease of RhoA in the melanosomes. Therefore the signal from ACTH will also have the increased level of an active Src-kinase. Then ACTH stimulates synthesis of glucocorticoids which action is directed first of all to strengthening of RhoA in tissues because the lack of a hydrocortisone leads to dispersion of a pigment, and enough quantity normalizes this process. Accumulation of glucocorticoids will cause increase in the RhoA expression in tissues It will prevent the further strengthening of an active Src-kinase of ACTH that will lead to the block of glucocorticoids production. At the same time, increase of RhoA activity of the signal coming from the hypothalamus nuclei will prevent the increase in the active Src-kinase of ACTH that will lead to the block of ACTH synthesis in the pituitary.

During the intensifying of the cells spasm and depression of an inactive Src-kinase and general RhoA activity of a brain with aging, the signal from a hypothalamus will be lower, than at young people therefore the low RhoA expression of a signal doesn't prevent the synthesis of ACTH, which therefore will be more prolonged. Further ACTH stimulates glucocorticoids which won't be able to block adequately ACTH because RhoA of the glucocorticoids signal will be insufficient to block a high Src-kinase of ACTH. As the result, the synthesis of glucocorticoids which stimulate RhoA in tissues increases. with aging.

Because the nervous tissue has rather high RhoA expression, additional influence of the increased quantity of glucocorticoids leads to the cell spasm and depression of proliferative activity. At young age this effect of glucocorticoids is canceled by estrogens as they activate the Src-kinase and inactivate a part of RhoA protein that promotes proliferative activity of cells.

Therefore, the chain of ACTH and glucocorticoids synthesis regulation is the following: RhoA – active Src - RhoA. Here it is necessary to add a regulation link from a suprachiasmatic nucleus of the hypothalamus (SCN) which controls circadian rhythms. In the afternoon the light from photoreceptors and the melanopsin cells of a retina strongly activates the Src-kinase in SCN because the Src-kinase is a redox-sensitive molecule [1, 5]. Then this signal is transmitted consistently to the hypothalamus neurons developing a releasing-factor, further to the pituitary and adrenal glands. Therefore the chain of regulation finally will have such view: active Src-RhoA-active Src-RhoA.

Thus, the level of RhoA and an inactive Src-kinase in an organism will be the highest at night when the parasympathetic nervous system generally works. In the afternoon and with aging the amount of these proteins decreases. Therefore during aging the quantity of mediators with a high expression of RhoA and an inactive Src-kinase, first of all mediators of a parasympathetic nervous system, especially acetylcholine and also dopamine, etc. decreases. Falling of the inactive Src-kinase level in the hippocampus and olfactory bulbs cells leads to decrease of cambial cells number in the germinal regions of a brain, to depression of nervous cells cytoskeleton and their processes formation and also pigment production function.

## 4. CONCLUSION

The research has shown that the germinal region of a brain, in particular of the hippocampus and olfactory bulbs as well as other organism tissues, is composed of morphofunctional zones-type structures. Proliferation of cells in one zone subunit happens not simultaneously: first the first 6 cells, and then the other 6 divide. The differentiation of daughter cells occurs in the electric field excited by 12 pairs of mother and daughter cells. The germinal region includes not only a subventricular area, but also sites near vessels to which cambial cells from peripheral blood arrive. Despite this the quantity of cambial cells of the olfactory bulbs and the hippocampus falls with aging. It is connected with the decrease in a share of an inactive Src-kinase and RhoA in all germinal loci of organs including a brain. Thus the formation of neurons cytoskeleton and their processes suffers, the spasm of cells increases and the proliferative activity of cambial cells falls. It in turn will lead to violation of associative communications between neurons. In the hippocampus decrease in proliferative activity of cambial cells is expressed more than in the olfactory bulbs due to the influence of glucocorticoids which strengthen a spasm of cells and by that continue to reduce the proliferation of cells.

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