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The effect of changes in *limk1* gene expression in dopaminergic and serotonergic and *fruitless* neurons on memory in *Drosophila melanogaster*

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Abstract. The actin cytoskeleton plays an important role in the formation and preservation of memory. LIMK1 is a key enzyme in the actin remodeling cascade. Changes in the expression of the *limk1* gene can lead to neurocognitive pathologies. A convenient model object for studying memory is *Drosophila melanogaster*. The conditioned courtship suppression paradigm is the most physiological approach to analyzing memory formation and preservation processes in *Drosophila*. The following brain structures are involved in the realization of memory processes in *Drosophila*: the antennal lobes, the protocerebrum, the mushroom bodies, and the central complex. The *Drosophila* brain contains about 140,000 neurons. Among them, dopaminergic and serotonergic neurons play an important role in the regulation of learning and memory processes. Involvement in memory processes is also shown for *fruitless* neurons, which are responsible for the mating behavior of males. We have studied the features of memory formation and preservation in male *Drosophila* with the activation and suppression of the expression of the *limk1* gene in dopaminergic and serotonergic neurons, as well as in *fruitless* neurons. We also analyzed the *Drosophila* brain structures responsible for memory processes in which the change in *limk1* expression had the greatest effect on protein fluorescence intensity.

Keywords: *limk1*, *Drosophila melanogaster*, dopaminergic and serotonergic neurons, *fruitless* neurons, memory

Изменения экспрессии гена *limk1* в дофаминергических и серотонинергических нейронах и нейронах *fruitless* влияют на память у *Drosophila melanogaster*

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Аннотация. Важную роль в формировании и сохранении памяти играет активный цитоскелет. Ключевым ферментом каскада ремоделирования актина является LIMK1. Изменение экспрессии гена *limk1* может привести к нейрокогнитивным патологиям. Удобным модельным объектом для изучения памяти является *Drosophila melanogaster*. Наиболее физиологичной методикой для анализа процессов формирования и сохранения памяти у дрозофилы является методика подавления ухаживания. В реализацию процессов памяти у дрозофилы вовлечены следующие структуры мозга: антеннальные доли, протоцеребрумы, грибовидные тела и центральный комплекс. Мозг дрозофилы содержит около 140 тысяч нейронов. Среди них ведущую роль в реализации процессов памяти играют дофаминергические и серотонинергические нейроны. Также вовлечённость в процессы памяти показана для немногочисленных нейронов *fruitless*, которые отвечают за поведение самцов во время ухаживания. Нами изучены особенности формирования и сохранения памяти у мух линий с активацией и подавлением экспрессии гена *limk1* в дофаминергических и серотонинергических нейронах, а также в нейронах *fruitless*. Также проанализировано, в каких структурах мозга дрозофилы, ответственных за реализацию процессов памяти, изменение экспрессии гена *limk1* оказало наибольшее влияние на интенсивность флуоресценции белка.

Ключевые слова: *limk1*, *Drosophila melanogaster*, дофаминергические и серотонинергические нейроны, нейроны *fruitless*, память

Introduction

According to the World Health Organization, the number of people suffering from dementia is increasing every year. Dementia refers to a number of diseases that negatively affect behavior, memory, and other cognitive functions. One of the pathological characteristics of cognitive dysfunction is the loss of dendritic spines of neurons (Yang et al. 2018). Dendritic spines are postsynaptic membrane structures that play a key role in synaptic plasticity, which forms the basis of learning and memory. The actin cytoskeleton is extremely important for the formation of dendritic spines. It is represented by two forms of actin: polymerized F-form and monomeric G-form. F-actin is able to depolymerize to G-actin, and G-actin can polymerize to F-actin under the action of the Rac1/cofilin signaling pathway. Rac1 phosphorylates p21-activated kinases (PAK), which promote the phosphorylation of LIM kinase 1 (LIMK1). LIMK1 inactivates cofilin by phosphorylating it, which leads to a change in the structure of actin. Inactivation of cofilin is known to lead to decreased learning and cause severe behavioral abnormalities (Kovaleva et al. 2019). Thus, impaired LIMK1 synthesis affects cofilin activity and synaptic plasticity underlying learning.

To understand the role of LIMK1 in the realization of learning and memory processes, animal model studies are needed, which make it possible to explore these processes at both the behavioral and molecular genetic level. According to the analysis of the nucleotide sequence, a convenient model object for comprehensive study is *Drosophila melanogaster*. The *limk1* gene of *Drosophila melanogaster* has 71% homology with the similar *Homo sapiens* gene. Earlier studies have shown differences in learning ability, as well as in the dynamics of forgetting in stocks polymorphic for the *limk1* gene, which also had different levels of LIMK1 isoforms (Kaminskaya et al. 2012; Nikitina et al. 2024). The expansion of knowledge and technology development in molecular biology and genetics enable the creation of transgenic *Drosophila* stocks with altered *limk1* gene expression. The short life cycle of *Drosophila melanogaster* makes it possible to conduct research at this facility in a short time. The molecular mechanisms of the main forms of mammalian learning are similar to those of *Drosophila*, which makes it possible to extrapolate the data obtained in relation to humans.

The most physiological approach to studying memory for *Drosophila* is the conditioned courtship suppression paradigm. We used it to analyze the processes of memory formation and preservation. This method is based on the courtship of a virgin male for a fertilized female. Males' courtship is

regulated primarily by olfactory and gustatory sensory systems and is initiated in a non-contact manner, by visual and olfactory stimuli. In this case, the male performs a number of actions: orients himself in relation to the female, touches her with his front paws (taste perception of cuticle pheromones occurs), retracts his wing, performs a 'mating song', touches the female's genitals, and licks them (receives additional information about pheromones). The female's behavior, as well as the composition of pheromones on the cuticle after mating, differs from those of the virgin female. The fertilized female rejects the male's courtship, and the male-specific pheromone cVA (cisvacenyl acetate) is present on her cuticle. After an unsuccessful experience in courting a fertilized female, the male significantly reduces the subsequent courtship of other females. The male learns during training, which results in memory formation (Kamyshev et al. 1999).

In *Drosophila*, the most important structures responsible for learning and memory are mushroom bodies and the central complex. At the same time, γ lobes participate in the formation of short-term memory, and α and β lobes of mushroom bodies participate in the formation of long-term memory (Redt-Clouet et al. 2012). In addition, antennal lobes, innervated by olfactory receptors and the protocerebrum, are also involved in the learning process. The protocerebrum regions responsible for courtship receive innervation from antennal lobes, as well as from the lobes of mushroom bodies indirectly through outgoing neurons (Zhuravlev et al. 2015).

In brain structures, neurons are distinguished, for which a high degree of involvement in learning and memory processes is shown. The *Drosophila* brain contains about 140,000 neurons. Among them, dopaminergic neurons have the greatest influence on the processes of memory formation and preservation. Studies have shown that specific clusters of dopaminergic neurons regulate the activity of synaptic outputs of mushroom bodies and are also involved in the formation of olfactory memory and its erasure (Keleman et al. 2012). Dopamine is also thought to provide different kinds of learning, including aversive olfactory learning and courtship suppression. Dopamine is important for guiding immediate responses to beneficial and harmful stimuli and simultaneously writing memories for future reference (Mohammad et al. 2024). In addition, it has been shown that serotonin and specific serotonin receptors are necessary for the correct realization of olfactory aversive memory (Johnson et al. 2011). Serotonin may also be crucial for associative learning in insects (Sitaraman et al. 2008) and modify different aspects underlying the formation of navigational memories (Gajardo et al. 2023). It has previously been shown that low levels

of LIMK1 in dopaminergic and serotonergic neurons promote learning, but not the formation of medium-term memory (Medvedeva et al. 2022). *Fruitless* neurons are also involved in memory processes, which are responsible for the behavior of males during courtship. About 300 γ lobe neurons of mushroom bodies and aSP13 dopaminergic neurons that regulate courtship and memory are classified as Fru-positive (Zhao et al. 2018). The involvement of various types of neurons in the realization of memory processes is due, among other things, to their ability to form dendritic spines, which are based on the actin cytoskeleton, the key enzyme of the remodeling cascade of which is LIMK1.

The aim of our research was to study the effect of changes in *limk1* gene expression in dopaminergic, serotonergic, and *fruitless* neurons on memory processes, as well as on the intensity of LIMK1 protein fluorescence in the brain of *Drosophila melanogaster*.

Materials and methods

The work was carried out on flies from the Center for Collective Use 'Biocollection of the IF RAS for the Study of the Integrative Mechanisms of the Activity of the Nervous and Visceral Systems'. We used *Drosophila* Gal4 > UAS stocks with suppression and activation of *limk1* gene expression in dopaminergic and serotonergic neurons, as well as in *fruitless* neurons. Stocks without expression changes were used as a control. The stocks were taken from Bloomington *Drosophila* Stock Center (BDSC), USA. Females expressing Gal4 in a specific nerve cell type were crossed with males carrying the *limk1* or dsRNA gene under control of the UAS sequence. The following strains were used:

No. 7009 (BDSC): w[1118]; P{w[+mC]=Ddc-GAL4.L}Lmpt[4.36]. GAL4 is expressed in dopaminergic and serotonergic neurons;

No. 30027 (BDSC): w[1118]; P{w[+mW.hs]=GawB}fru[NP0021]. GAL4 is expressed in *fruitless* neurons regulating mating behavior;

No. 26294 (BDSC): y[1] v[1]; P{y[+t7.7]v[+t1.8]=TRiP.JF02063}attP2. The strain expresses interfering RNA against *limk1* (RNAi) under the control of the UAS regulatory sequence;

No. 9116 (BDSC): y[1] w[*]; P{w[+mC]=UAS LIMK1.T:lvir\HA1}M6. The strain expresses LIMK1 under the control of the UAS regulatory sequence;

No. 36303 (BDSC): y[1] v[1]; P{y[+t7.7]=CaryP}attP2. The control strain with genetic background identical to that of No. 26294 and # 9116, but lacking RNAi and LIMK1.

The following crosses were carried out:

1. ♀7009 × ♂26294 — suppression of the *limk1* gene in dopaminergic and serotonergic neurons.

2. ♀7009 × ♂9116 — activation of the *limk1* gene in dopaminergic and serotonergic neurons.

3. ♀7009 × ♂36306 — control: no changes in the expression of the *limk1* gene in dopaminergic and serotonergic neurons.

4. ♀30027 × ♂26294 — suppression of the *limk1* gene in *fruitless* neurons.

5. ♀30027 × ♂9116 — activation of the *limk1* gene in *fruitless* neurons.

6. ♀30027 × ♂36306 — control: no changes in the expression of the *limk1* gene in *fruitless* neurons.

Conditioned courtship suppression paradigm

According to the conditioned courtship suppression paradigm, a five-day-old virgin male was placed in a special chamber together with a fertilized female of the *Canton-S* wild-type stock for 30 minutes (training). Virgin males were used as a control. Trained and virgin males were tested at 0, 15, 30 minutes and 1, 2, 3, and 24 hours after training. The observation time was 300 seconds. With the help of a special program, the start and end times of behavioral elements associated or not related to courtship were recorded. To assess the ability to form and preserve memory, the learning index (LI) was calculated at all time intervals using the following formula: $LI = (CI_n - CI_t) / CI_n \times 100\%$, where LI is the learning index, CI_n is the average courtship index of naïve males, and CI_t is the average courtship index of trained males. The courtship index (CI) was calculated as the courtship time of the male for the female, expressed as a percentage of the total observation time. 20 pairs of flies were tested in each group. A two-way randomization test was used for statistical data processing (Kamyshov et al. 1999).

Analysis of LIMK1 distribution

To identify the *Drosophila* brain structures responsible for memory processes, where the change in *limk1* expression had the greatest impact on the level of LIMK1 protein, we evaluated protein distribution in the following structures: antenna lobes, upper medial protocerebrum, α , β , γ lobes, and pedunculus of mushroom bodies, as well as in the ellipsoid body of the central complex. As part of preparations, five- to seven-day-old males were subjected to cold anesthesia and pinned to a gelatin substrate in a Petri dish. The brains were extracted in a PBS buffer (pH 7.5) using sharp tweezers (Merck, T4412), accumulated in the same buffer in the cold and then fixed in 4% paraformaldehyde on PBS for 1 hour at room temperature. The antibodies were diluted in 0.2% TBStween at a ratio of 1:200. Incubation was carried out at 4 °C for 3 days with primary antibodies and for 1 day with secondary antibodies. Primary rat anti- LIMK1 antibodies

(Enzo Life Sciences, ALX-803-343-C100) and secondary donkey antibodies anti-rat Alexa Fluor 594 (Thermo Fisher Scientific, A-21209) were used. For additional imaging, primary mouse antibodies to *Drosophila* cysteine string protein (CSP) (courtesy of Professor Eric Buchner, Institute of Clinical Neurobiology, Würzburg) and secondary goat antibodies anti-mouse, AlexaFluor 488 (Invitrogen, A32723) were also used. The brains were enclosed in a Vectashield medium containing DAPI (Vector laboratories, H-1200-10). The brain was scanned frontally using laser scanning confocal microscopy LSM 710 Carl Zeiss, CCP 'Confocal Microscopy' Pavlov Institute of Physiology of the Russian Academy of Sciences. The experiment included 3 repetitions. Scanning was performed using an X63 lens at different depths (z-step of 2 microns). The images were analyzed using the Fiji software. The brain structures were visually determined using the online atlas of the drosophila brain (Virtual Fly Brain). To measure the average level of LIMK1 in brain structures, the average signal intensity was analyzed in three small square areas ($\sim 10 \times 10$ microns) within each structure. The average values obtained were normalized to the average intensity of the structure for each brain. The auto contrast function was used to prepare the drawings for each optical slice. The average LIMK1

level was analyzed using the Kruskal-Wallis criterion, followed by a posteriori pairwise comparisons using the Mann-Whitney U-test.

Real-time PCR assay

The change in *limk1* expression in the test stocks was evaluated by real-time PCR with reverse transcription. PCR was performed using a mixture of qPCRMix-HS (Evrogen, PK156L) using the StepOnePlus Real system Time PCR System (Applied Biosystems). RT-qPCR primers for *limk1* amplification were designed in this study with the following sequences: Forward 5'-GTGAACGGCA-CACCAGTTAGT-3', Reverse 5'-ACTTGCACCG-GATCATGCTC-3'. The experiment included 5 repetitions. The Mann-Whitney U-test was used for statistical data processing.

Results and discussion

Analysis of LI in stocks with altered *limk1* gene expression in dopaminergic and serotonergic neurons showed that *limk1* suppression reduces the ability to form memory. The LI does not significantly differ from zero immediately after training (Fig. 1). *limk1* activation does not affect the ability to form memory, but affects the ability to retain it:

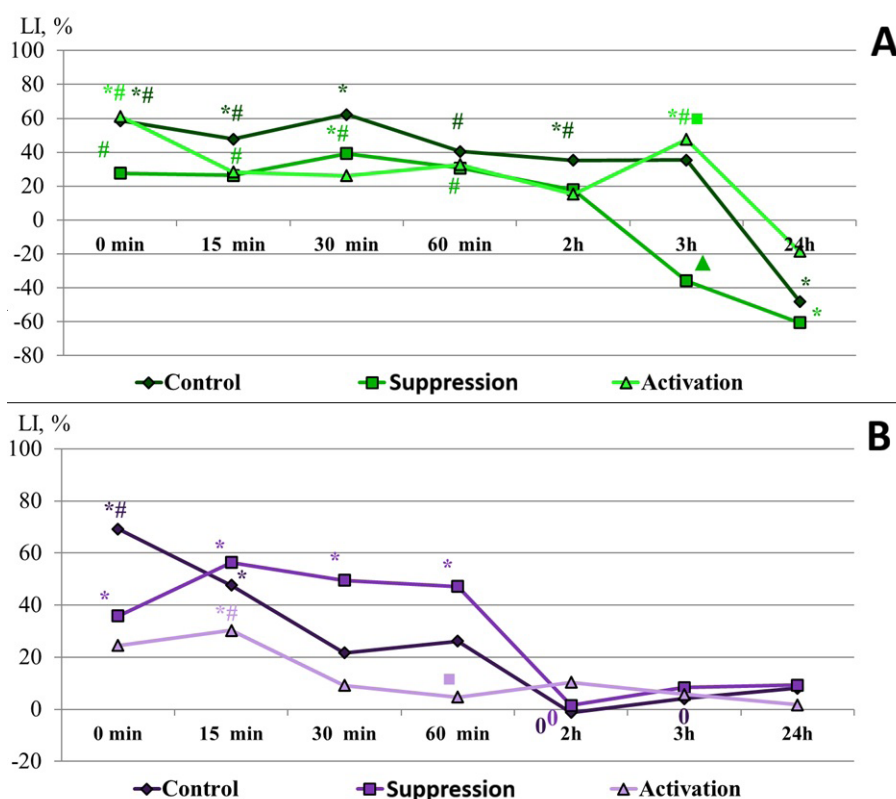


Fig. 1. Learning indices of *Drosophila melanogaster* stocks with altered *limk1* gene expression. A — in dopaminergic and serotonergic neurons, B — in *fruitless* neurons. On the abscissa axis: the time after the end of the training, on the ordinate axis: LI (learning index). * — significantly different from zero, # — significantly different from 24 h, 0 — significantly different from 0 min, ▲ — significantly different from the control, ■ — significantly different from the suppression of *limk1* gene ($p \leq 0.05$, two-way randomization test)

at the initial stages, a decrease in LI happens faster than in the control, but then slows down.

The analysis of LI in stocks with a change in *limk1* gene expression in *fruitless* neurons showed that flies of the control stock are able to retain memory for up to 15 minutes. Suppression of *limk1* restores memory for an interval of 30–60 minutes, and then the LI decreases to the control level. In stocks with *limk1* activation, memory was impaired at all time intervals, and the dynamics of LI change was less pronounced than in the control.

In stocks with Gal4 drivers active in dopaminergic and serotonergic neurons, when suppressing *limk1*, the level of this RNA was significantly lower than in the control, and when activated, it was higher than in the control and when *limk1* was knocked down. In stocks with altered expression

in *fruitless* neurons, when *limk1* was suppressed, the RNA level was significantly lower than in the control.

A comparative analysis of the distribution of LIMK1 protein in the brain structures of stocks with a driver Gal4 in dopaminergic and serotonergic neurons showed that upon *limk1* activation, the intensity of protein fluorescence in the upper medial protocerebrum was significantly higher than in the control and suppression (Fig. 2). In stocks with Gal4 drivers in *fruitless* neurons, when *limk1* was activated, the protein level in the ellipsoid body was higher than in the control. No other significant differences were found. Figs. 3 and 4 show micrographs illustrating the distribution of LIMK1 in the brain of adult *Drosophila* with a change in *limk1* gene expression.

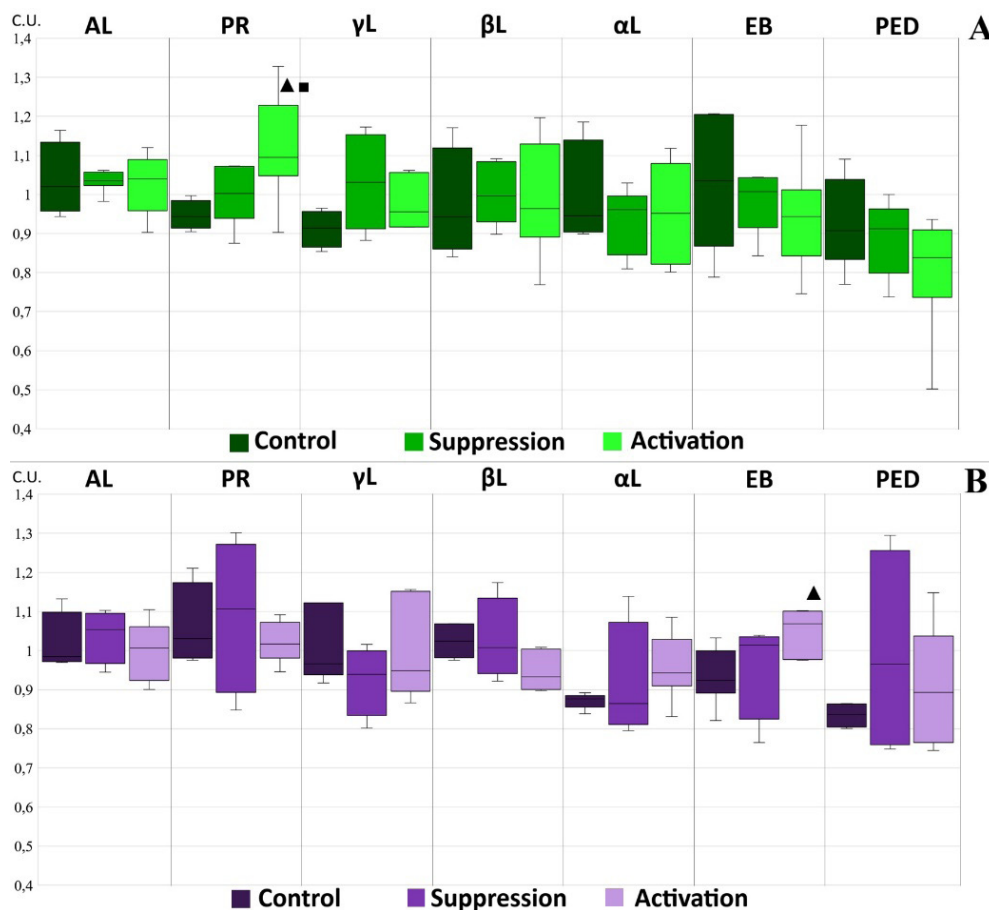


Fig. 2. The intensity of LIMK1 fluorescence of *Drosophila melanogaster* with a change in *limk1* gene expression. A — in dopaminergic and serotonergic neurons, B — in *fruitless* neurons. On the abscissa axis: the intensity of LIMK1 fluorescence in C.U. (conventional units), on the ordinate axis: the structures of the *Drosophila* brain: AL — antennal lobes, PR — protocerebrum, αL — α lobes of mushroom bodies, βL — β lobes of mushroom bodies, γL — γ lobes of mushroom bodies, EB — ellipsoid body, PED — peduncle. ▲ — significantly different from the control, ■ — significantly different from the suppression of *limk1* gene ($p \leq 0.05$, Mann–Whitney U test)

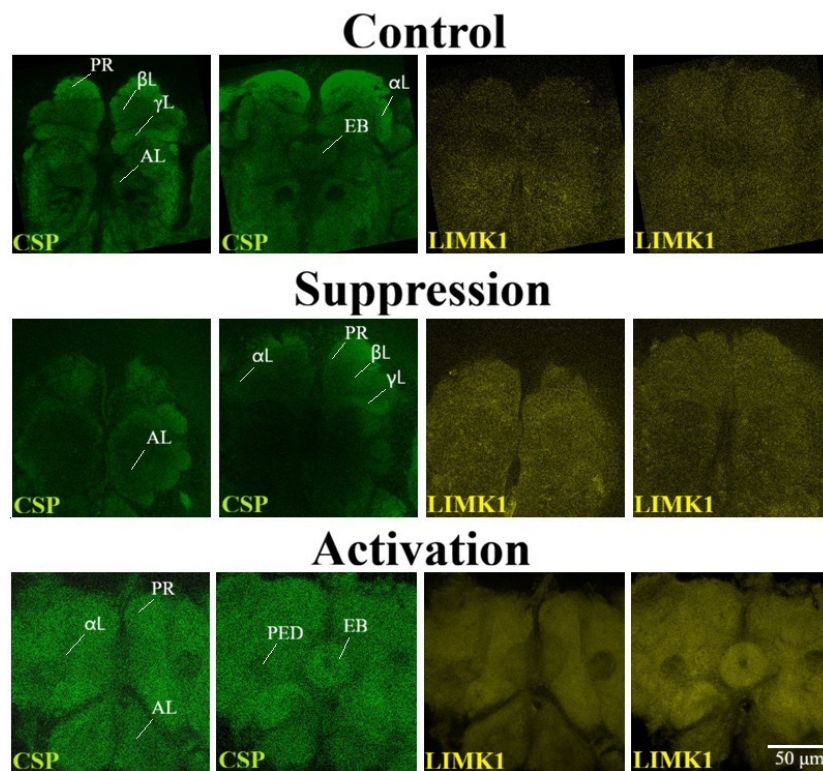


Fig. 3. LIMK1 distribution in the brain of adult *Drosophila* with a change in *limk1* gene expression in dopaminergic and serotonergic neurons. The green color is CSP, and the yellow color is LIMK1. AL — antennal lobes, PR — protocerebrum, αL — α lobes of mushroom bodies, βL — β lobes of mushroom bodies, γL — γ lobes of mushroom bodies, EB — ellipsoid body, PED — peduncle

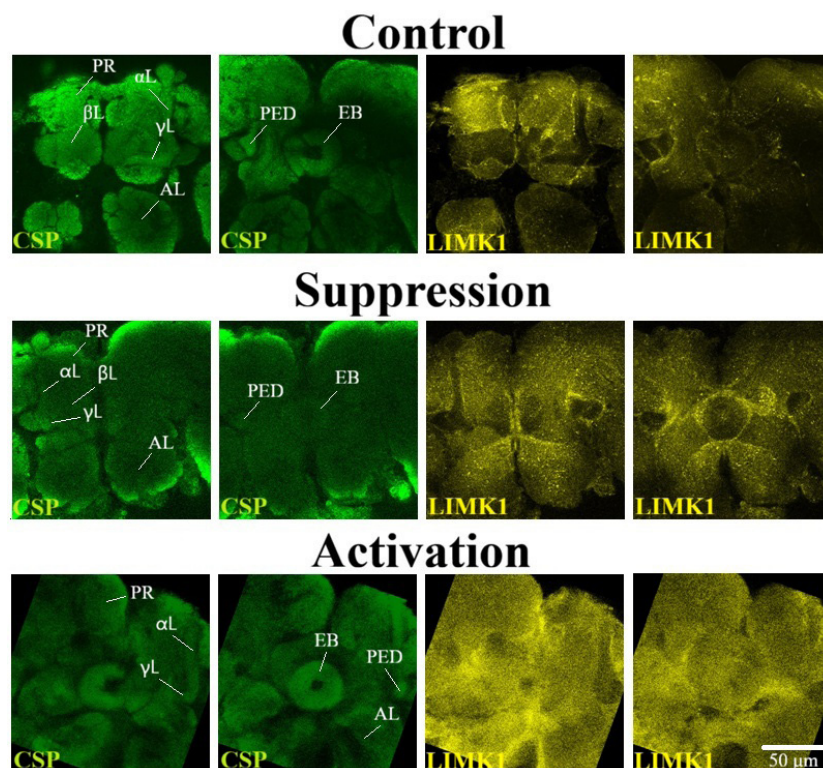


Fig. 4. LIMK1 distribution in the brain of adult *Drosophila* with a change in *limk1* gene expression in *fruitless* neurons. The green color is CSP, and the yellow color is LIMK1. AL — antennal lobes, PR — protocerebrum, αL — α lobes of mushroom bodies, βL — β lobes of mushroom bodies, γL — γ lobes of mushroom bodies, EB — ellipsoid body, PED — peduncle

Conclusion

Thus, a change in the expression of the *limk1* gene in different types of neurons has a multidirectional effect on the processes of memory formation and preservation in the studied stocks, yet similarly affecting changes in the intensity of LIMK fluorescence. Suppression of *limk1* gene expression in dopaminergic and serotonergic neurons negatively affects the ability to form memory, while suppression in *fruitless* neurons does not determine the ability to form, though positively affecting the ability to retain memory. LIMK1 suppression had no significant effect on the intensity of LIMK1 fluorescence in different brain structures. It can be assumed from immunohistochemistry data that activation of *limk1* gene expression in the dopaminergic and serotonergic neurons of the protocerebrum exacerbates the processes of forgetting. At the same time, activation of *limk1* gene expression in *fruitless* ellipsoid body neurons suppresses the ability to memory formation.

Local changes in *limk1* expression in different neurons of the *Drosophila melanogaster* brain can significantly affect the ability to form and preserve memory (Zhuravlev et al. 2024). The use of transgenic stocks reveals the effect of the expression of various genes in certain structures of the *Drosophila* brain on learning and memory processes. Memory retention requires a proper balance of *limk1* activity in different types of neurons and brain structures in *Drosophila melanogaster*. Such studies open up prospects for studying the interactions of proteins and signaling cascades that play a role in the development of cognitive dysfunctions.

Conflict of Interest

The authors declare that there is no conflict of interest, either existing or potential.

Конфликт интересов

Авторы заявляют об отсутствии потенциального или явного конфликта интересов.

Author Contributions

- a. Ekaterina S. Zalomaeva — data collection, data processing, writing and editing the manuscript, visualization;
- b. Ekaterina S. Egozova — data collection, data processing;
- c. Aleksandr V. Zhuravlev — data collection, data processing;
- d. Anna V. Medvedeva — data collection, data processing;
- e. Svetlana A. Vasilieva — data collection, data processing;
- f. Ekaterina A. Nikitina — conceptualization and experimental design, writing and editing the manuscript.

All the authors have read and agreed to the published version of the manuscript.

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