論文 / 著書情報
Article / Book Information

題目(和文)	後シナプスにおけるヒスタミン受容体の神経活動依存的な抑制制御
Title(English)	Activity-dependent synaptic plasticity through regulation of histamine receptor in the Drosophila visual system
著者(和文)	BaiYiming
Author(English)	Yiming Bai
出典(和文)	学位:博士(理学), 学位授与機関:東京工業大学, 報告番号:甲第11718号, 授与年月日:2022年3月26日, 学位の種別:課程博士, 審査員:鈴木 崇之,一瀬 宏,粂 昭苑,廣田 順二,増田 真二
Citation(English)	Degree:Doctor (Science), Conferring organization: Tokyo Institute of Technology, Report number:甲第11718号, Conferred date:2022/3/26, Degree Type:Course doctor, Examiner:,,,,
学位種別(和文)	博士論文
Category(English)	Doctoral Thesis
種別(和文)	論文要旨
Type(English)	Summary

（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

系・コース： Department of, Graduate major in	生命理工学　系 生命理工学　コース	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of	（　理学　）
学生氏名： Student's Name	Bai Yiming	指導教員（主）： Academic Supervisor(main)	鈴木　崇之	
		指導教員（副）： Academic Supervisor(sub)		

要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

'Plasticity' allows animals to develop mature brains, recover from injury, and respond to various stimuli and experiences from the environment through modifying the structure, connection, or molecular process in their brains. The plasticity occurring during adaption happens in different scales, including cellular scale and subcellular scale. On a subcellular scale, plasticity occurs at the sites where neurons make connections with each other known as synapses. Activity-dependent synaptic plasticity is believed to be critical for responses to the environment and adaptive behaviors. When a circuit receives input activity, direct synaptic changes occur and have subsequent consequences in the circuit. It still requires more studies on how synaptic plasticity affects the circuit change. One type of presynaptic neuron usually has connections with various types of postsynaptic neurons. It remains a big question whether synaptic plasticity happens among all the connections, or only some specific subsets of postsynaptic neurons change the connections with the presynaptic neuron and modify their activity responses according to input activity.

For the activity-dependent plasticity research at the synaptic level, plenty of genetic tools and experimental methods have been developed in model animal *Drosophila Melanogaster*, which is also called 'fruit fly'. The *Drosophila* visual system is a powerful model to study the activity-dependent synaptic plasticity invoked by external stimulation from the environment. The adult *Drosophila* visual system comprises the retina and optic lobe, which consists of the lamina, medulla, lobula, and lobula plate. Approximately 750 small eyes, ommatidia, are present in the retina, each containing eight photoreceptor neurons (R1–8). R1–6 are responsible for light-sensing and motion detection, while R7 expresses UV- and R8 blue- and green-sensitive opsins. Photoreceptors in *Drosophila* mainly release inhibitory neurotransmitter histamine to their postsynaptic neurons.

In the adult *Drosophila* visual system, upon continuous light condition (LL), photoreceptor neurons, especially R8, reorganize synaptic components at the Active Zone (AZ) through microtubule destabilization. The activities of both pre- and postsynaptic neurons are involved in synaptic component reorganization. However, how the visual system adapts to different environmental experiences at a circuitry scale is unknown. Moreover, while the presynaptic side is intensely studied during synaptic plasticity, we know rather less about the postsynaptic side in the adult *Drosophila* visual system. To achieve a better understanding of the subsequent influence of activity-dependent synaptic plasticity caused by environmental stimulation to the circuitry in the *Drosophila* visual system, I applied a transcriptional reporter of intracellular calcium (TRIC) to monitor the activity of neurons postsynaptic to photoreceptors. The validation of postsynaptic physiological response showed that lamina monopolar neuron L2 tended to show more drastic activity response to environmental stimulation after activity-dependent synaptic plasticity caused by chronic light treatment in *Drosophila* visual system which was reversible if flies were returned to DD condition.

It attracted my interest in the underlying mechanism of response changes in the circuit to subsequent environmental stimulation following activity-dependent synaptic plasticity. Since histamine is the main and inhibitory neurotransmitter released by photoreceptors in *Drosophila* visual system, the expression level of histamine receptors (HRs) in L2 may account for the response change. I labeled HRs in postsynaptic L2 neurons and identified activity-dependent, transcriptional, reversible downregulation of HR in the medullar part of L2 neuron under LL condition. I found that HR decrease in L2 neurons was regulated by CaMKII and CREB-B. By contrast, histamine receptor downregulation does not occur in L1 upon prolonged light exposure, which is consistent with the result in TRIC assay that response changes happen only in L2, not in L1. I found that exogenous expression of Ort in L2 neurons attenuates the enhanced activity response caused by constant light exposure, which supports my hypothesis that the change in L2 activity response to 1-day photoreceptor activation after prolonged light exposure is derived from HR reduction. The activity of R1–6 was proved necessary for this histamine receptor regulation in L2 through *ninaE* mutation experiment. I confirmed synaptic connections between R8 and L2 in the medulla and found that activating R8 was sufficient to downregulate the histamine receptor level in L2. The activation of L2 was also proved to stabilize the presynaptic components in presynaptic R8 photoreceptors.

Hereby, I report that in the adult *Drosophila* visual system, after constant light exposure-induced synaptic plasticity, inhibitory neurotransmitter histamine receptor transcriptional downregulation occurs in the postsynaptic lamina neuron L2, but not L1, depending on the photoreceptor and postsynaptic neuronal activity and involving CaMKII and CREB-B. The histamine receptor transcriptional downregulation results in a more intense postsynaptic L2 neuronal response to subsequent environmental stimulations, especially in the medulla. This research succeeded to visualize the circuit change process after synaptic plasticity according to long-term activation and find in vivo evidence of the circuitry plasticity. Findings in this research deepen the understanding of the consequence of activity-dependent synaptic plasticity to the circuit and provide new insights into the activity-dependent synaptic plasticity mechanism in the neural circuit.