氏　　名	戸崎浩和
学位（専攻分野）	博士(理学)
学位記番号	総研大甲第768号
学位授与の日付	平成１６年３月２４日
学位授与の要件	生命科学研究科　遺伝学専攻 学位規則第４条第１項該当
学位論文題目	Computational analysis of olfactory neural networks by an activity-dependent self-organization model
論文審査委員	主　査　教授　相賀　裕美子 教授　菅原　秀明 教授　廣海　健 助教授　高野　敏行 チームリーダー　田中　繁（理化学研究所）

論文内容の要旨

The olfactory sensory neuron (OSN) is the primary neuron of the olfactory system. It expresses odorant receptors (ORs) which catch odorant molecules. There are about 1000 types of ORs. An OSN expresses only one type of ORs, and therefore there are about 1000 types of OSNs. OSNs project to mitral cells in the olfactory bulb, which are the secondary neurons of the olfactory system. The cell bodies of the same type of OSNs scatter on the olfactory epithelium, but the axons from the same types of OSNs converge to a small number of mitral cells, and dendrites of the mitral cells and axon terminals of the OSNs collectively construct a mass called the glomerulus. There are more than 1800 glomeruli in an olfactory bulb. A single type of OSNs construct about 1~4 glomeruli per the bulb. How do the same types of OSN axons converge? A theory which is supported by many molecular biologists is that OSN axons are guided by guidance molecules. Certainly, guidance molecules are very important for the OSN axon guidance. It is experimentally revealed that a few guidance molecules and their receptors are expressed in the olfactory system, but guidance molecules enough to guide about 1000 types of OSN axons to their precise targets are not discovered. The guidance molecules which have been discovered by now only have simple functions attracting or repulsing axons which express their receptors. If OSN axons were completely guided to their precise targets only by these guidance molecules, several hundred guidance molecules or a completely new mechanism to efficiently guide OSN axons would be necessary.

Here I suggest that the OSN axon convergence is governed by an activity-dependent mechanism. The activity-dependent mechanism is often used to explain for the formation of the ocular dominance column. The mechanism is based on the Hebb's rule. When presynaptic and postsynaptic neurons are activated at the same time, the synapses between them are strengthened. In other words, when a postsynaptic neuron receives inputs from multiple presynaptic neurons, and if many presynaptic neurons make action potentials at the same time, the postsynaptic neuron will be easily beyond the

The olfactory sensory neuron (OSN) is the primary neuron of the olfactory system. It expresses odorant receptors (ORs) which catch odorant molecules. There are about 1000 types of ORs. An OSN expresses only one type of ORs, and therefore there are about 1000 types of OSNs. OSNs project to mitral cells in the olfactory bulb, which are the secondary neurons of the olfactory system. The cell bodies of the same type of OSNs scatter on the olfactory epithelium, but the axons from the same types of OSNs converge to a small number of mitral cells, and dendrites of the mitral cells and axon terminals of the OSNs collectively construct a mass called the glomerulus. There are more than 1800 glomeruli in an olfactory bulb. A single type of OSNs construct about 1~4 glomeruli per the bulb. How do the same types of OSN axons converge? A theory which is supported by many molecular biologists is that OSN axons are guided by guidance molecules. Certainly, guidance molecules are very important for the OSN axon guidance. It is experimentally revealed that a few guidance molecules and their receptors are expressed in the olfactory system, but guidance molecules enough to guide about 1000 types of OSN axons to their precise targets are not discovered. The guidance molecules which have been discovered by now only have simple functions attracting or repulsing axons which express their receptors. If OSN axons were completely guided to their precise targets only by these guidance molecules, several hundred guidance molecules or a completely new mechanism to efficiently guide OSN axons would be necessary.

Here I suggest that the OSN axon convergence is governed by an activity-dependent mechanism. The activity-dependent mechanism is often used to explain for the formation of the ocular dominance column. The mechanism is based on the Hebb's rule. When presynaptic and postsynaptic neurons are activated at the same time, the synapses between them are strengthened. In other words, when a postsynaptic neuron receives inputs from multiple presynaptic neurons, and if many presynaptic neurons make action potentials at the same time, the postsynaptic neuron will be easily beyond the

threshold and activated together. As a result, the synapses made by the presynaptic neurons which are similarly activated and project in the vicinity are strengthened, and therefore presynaptic neurons which show similar activities converge their axons. This rule is applicable to the convergence of the same types of OSN axons. In the present paper I used Tanaka's activity-dependent self-organization model. This model is constructed by adopting the thermodynamic theory in the Hebb's rule. This model compares the state of combinations between presynaptic and postsynaptic neurons to energy. In high energy, presynaptic neurons randomly project to postsynaptic neurons, but as the energy decreases, the same types of presynaptic neurons converge according to the Hebb's rule. In the case of ocular dominance column, this model faithfully reproduced that two types of presynaptic neurons are segregated into stripes.

When I adopted this model for the olfactory system and simulated, the same types of OSN axons converged and constructed glomeruli. In living animals, glomerulus positioning between individuals of the same genetic backgrounds is slightly different. I reproduced this phenomenon reasonably by the activity-dependent model. The biggest difficulty for an activity-dependent mechanism to explain the OSN targeting was the results of the knockout mice for Olfactory Cyclic nucleotide Gated Channel 1. I reproduced the glomerulus map, assuming a very weak activity correlation of OSNs of the mutant animals. Furthermore, the activity-dependent model explained the results of OR transgenic and knockout mice, and double glomeruli although it is difficult that guidance molecules explain all of these results reasonably.

I also examined how the postsynaptic interaction function and the activity correlation of OSNs influenced the glomerular size. In the olfactory system, OSNs have complicated activity correlations unlike the neurons in the ocular dominance column because of complicated overlaps between receptive ranges of different types of ORs. Postsynaptic interaction function was expressed by sum of two Gausian functions. One expressed exciting input and the other expressed inhibiting input. The sum of the two

functions made the curve like a Mexican hat, and I examined how glomerulus size was altered with the change of the curve. Basically, the glomerular size increased in proportion to widing of the positive interactions in the curve. The glomerular size in the simple OSN correlation where crosstalk between ORs was not considered was larger than in the complicated OSN correlation where many different types of ORs showed overlapping reactions to the same odorants. I also suggest that this activity dependent model can explain the targeting of the vomeronasal receptor neurons to the accessory olfactory bulb (AOB). Glomeruli in the AOB are smaller than those in the olfactory bulb. I assumed that this was because mitral cells in the AOB project multiple dendrites to several glomeruli, and the distance of excitatory postsynaptic interactions was small, and with this assumption, reproduced the glomerular map in the AOB. Furthermore, I explained other experimental results of the AOB by this model.

In the olfactory system, an activity-dependent mechanism has been denied by many experimental researchers. However, much argument was not devoted to an activity-dependent mechanism. The present paper showed that an activity-dependent mechanism could support many experimental results.

論文の審査結果の要旨

嗅覚の1次ニューロンである嗅神経は数百万本あり匂い受容体を持っている。匂い受容体はマウスで約 1000 種類ほどあり1本の嗅神経にはただ1種類の匂い受容体が発現する。さらに 2 次ニューロンである僧帽細胞とのシナプス結合部位は糸球体という構造を形成し、一つの嗅球に糸球体は 1800 個ほど存在する。同じ匂い受容体を持つ嗅神経の細胞体は嗅上皮にばらばらに存在するが、その軸索は1個または数個の糸球体に集まって投射、つまり収束している。
今まで糸球体の形成には神経軸索ガイダンス分子が大きく寄与しているのではないかといわれてきが、これは 1000 種類ものガイダンス分子を新たに想定する必要がある上実際にそのような多様なガイダンス分子の報告もなく現実的ではないと考えられている。そこで戸崎君は、このような特徴的な糸球体の形成と配置に類似した現象を視覚系で見出し、視覚系を説明する Hebb の理論をもとにしてこれを嗅覚系に当てはめ、コンピュータシミュレーションにより糸球体形成の理論を説明した。このモデルは、嗅神経が糸球体にシナプスを形成する時に神経活動に依存する自己組織化能をもたせたもので、戸崎君はこのシミュレーションの条件を調節することにより、同じ嗅神経がクラスターをなして糸球体を形成しうることを示した。またこれまで自己組織化のモデルでは説明が困難とされていた OCNC1(嗅神経チャネル分子)ノックアウトマウスの表現型を説明することや嗅神経に発現するレセプターを他のレセプターと入れ替えたトランスジェニックマウスに見られる現象を再現することに成功した。以上のように、この論文の内容は、実験的に示された現象をよく説明できるモデルとして非常に優れており、学位に充分ふさわしい内容と判断した。

また公開発表会の後に、質疑応答がなされましたが、戸崎君は博士論文に関わる研究分野に関して充分な知識をもち、その知識に基づいて考察する能力を持つことが示された。またこの学位論文は英語で記載されており、さらに戸崎君はこの内容以外にもすでに論文を発表していることから英語の能力にも問題なく、審査員全員一致で学位にふさわしいと判断した。