receptor family. Odorant-bound ORs stimulate Gs-type G-proteins, Galpha-olf, which in turns activate cAMP-mediated signaling pathway in olfactory sensory neurons. To better understand the molecular basis for OR activation and G-protein coupling, we analyzed the effects of a series of site-directed mutations of a mouse OR, mOR-EG, on function. Thus, we identified amino acids involved in two steps of G protein activation by an OR, conformational changes within the OR and OR-G protein interactions. Our results provide insights into how ORs transition from an inactive to an active state, as well as where and how activated ORs interact with G-proteins. Recently, we have reported a rather surprising finding that insect ORs are not G protein-coupled receptors, but heteromeric ligand-gated ion channels. Despite the common function of the olfactory system as a chemosensor in various species, some differences between vertebrate and invertebrate appears to be found in properties of chemosignals, in receptor repertoire and their expression pattern, and in the mode of receptor signal transduction, which is likely a consequence of adaptation to the living environment during the processes of evolution.

## 2S10-2 嗅覚神経系の機能構築原理：嗅上皮から嗅球へ、さらには高次嗅覚中枢へ

Anatomical and functional architecture of the olfactory neural circuitry in zebrafish: from odor inputs to behavioral outputs

*Yoshihiro Yoshihara (Lab for Neurobiology of Synapse, RIKEN Brain Science Institute)*

Zebrafish is now becoming one of the most useful model organisms in neurobiology. In addition to its general advantageous properties (external fertilization, rapid development, transparency of embryos, etc.), the zebrafish is amenable to various genetic engineering technologies such as transgenesis, mutagenesis, gene knockdown, and transposon-mediated gene transfer. A transgenic approach unraveled two segregated neural circuits originating from ciliated and microvillous sensory neurons in the olfactory epithelium to distinct regions of the olfactory bulb, which likely convey different types of olfactory information (pheromones and odorants) to the higher olfactory centers. Furthermore, the two basic principles identified in mice, so-called “one neuron - one receptor rule” and “convergence of like axons to target glomeruli”, are basically preserved also in the zebrafish, rendering this organism a suitable model vertebrate for studies of the olfactory system. In this talk, I will summarize recent advances in our knowledge on genetic, molecular, and cellular mechanisms underlying the development and functional architecture of the olfactory neural circuits in the zebrafish that lead to specific odor-induced behaviors.

## 2S10-3 ショウジョウバエの味受容細胞におけるモーダルシフト

Cross-modality sensing in gustatory receptor neurons of Drosophila

*Teiichi Tanimura (Department of Biology, Graduate School of Sciences, Kyushu University)*

Olfactory sensilla of Drosophila are located at the antennal segment and the maxillary palp. Gustatory sensilla are located at the labellum and the tarsal segment of legs. Both sensilla house sensory receptor neurons expressing seven transmembrane receptors, ORs and GRs. We expressed olfactory receptor genes in taste neurons to know if they gain ability to respond to odors. To this end we utilized a tungsten electrode recording method that enable us to record nerve responses to an odor. We found that taste neurons respond to odors if OR is expressed together with an ubiquitous Or83b. These results suggest the functional similarity between taste and olfactory neurons. Employing the Gal4-UAS system we expressed Or genes either in sugar cells or in bitter cells. Depending on the cell type a different feeding effect of an odor was observed. Sex pheromones are volatile or non-volatile in Drosophila. Volatile pheromones are sensed by olfactory neurons and we found that labellar Gr66a-expressing bitter-sensing taste neurons respond to a male specific non-volatile pheromone, 7-tricosene. 7-Tricosene is probably sensed by tarsal taste sensilla during courtship and we observed projection patterns from Gr66a-expressing neurons in tarsi. Projection patterns of Gr66a-expressing neurons from sensilla that might sense the sex-pheromone and those from other sensilla that are involved in feeding behavior are different. These new results demonstrate a cross-modality sensing in taste neurons of Drosophila.

## 2S10-4 衣擦れが苦痛に変わるとき

Touch sensation causes abnormal pain

*Kazuhide Inoue.(Department of Molecular and System Pharmacology, Graduate School of Pharmaceutical Sciences, Kyushu University)*

Microglia are known as resident macrophages in the CNS. Microglia play a key role in neuropathic pain. Neuropathic pain is a severely disabling state that affects more than 15 millions of people in the world. This type of pain may be experienced after nerve injury. In the neuropathic pain state, touch stimulation frequently evokes strong pain sensation. We have shown that P2X4 receptors (P2X4Rs), which are upregulated in activated microglia in the spinal cord after nerve injury (Nature, 2003), and the stimulation of P2X4Rs causes release of brain-derived neurotrophic factor (BDNF) (Nature, 2005). BDNF causes a collapse of transmembrane anion gradient of lamina I neurons, resulting in the change of the inhibitory action of GABA to excitatory one. Thus, we postulate that BDNF released by the stimulation of P2X4Rs in microglia is a crucial signalling molecule for neuropathic pain. We also found that P2Y12 receptors and P2Y6 receptors are tightly related with not only chemotaxis or phagocytosis (Nature, 2007) but also the pain. These findings indicate that nucleotides play a key role in the communication between neuron and microglia.

## 3S1-1 はじめに：創薬の新局面と数理 ―数論の応用―

New aspects of drug discovery and its representation by number theory

*Kazuo Kuwata (Center for Emerging Infectious Diseases, Gifu Univ.)*

Recent development in NMR techniques enabled us to observe the slow dynamics on the time scale of micro- to milliseconds of nuclei in a protein. However, the nature of such a slow motion is not well understood. For example, at room temperature the time constant of the refolding of prion protein is about 100 microseconds, but that of slow dynamics is between sub-millisecond to milliseconds. During such a slow motion, the native structure has a chance to unfold completely. In order to describe the protein dynamics in a large phase space, here we have constructed a novel representation theory, which is essentially based on the number theory. We could represent the conformational rearrangement with an extremely low probability. This formalism includes the Dirichlet series to represent the partition function, which consists of periodic trajectories with prime number steps.

## 3S1-2 蛋白質準安定状態の同定からプリオン病治療薬開発へ

The low-lying excited states: from identification to drug discovery

*Yuji O. Kamatari (1). (1: Center for Emerging Infectious Diseases, Gifu Univ)*

Proteins are intrinsically dynamic, which lead to excursions from the highly-populated ground state to less-populated excited states. The excited states, especially meta-stable states energetically close to the ground state, are thought to play important roles in protein function, stability, aggregation, lifetime etc. We have investigated the low-lying excited (N') states of lysozyme [1] and prion protein [2] using high pressure NMR spectroscopy and NMR relaxation. These data indicated that the conformational fluctuations are closely related to the cavity and hydration. In the case of prion protein, conformational transition to the scrapie form may occur through the N' states. Therefore, we have designed compounds that fit into a pocket created by residues undergoing the conformational rearrangements between the ground and N' states and found compounds that efficiently reduced formation of the scrapie form *in vitro* and *in vivo* [3]. Surface plasmon resonance and heteronuclear NMR showed that these compounds specifically binding to the flexible region around the pocket of the native protein. There results indicated that decrease of the N' population hampers the pathogenic conversion process of prion protein. [1] Y. O. Kamatari et al. (2001) Eur. J. Biochem. 268, 1782. [2] K. Kuwata et al. (2004) Biochemistry 43, 4439. [3] K. Kuwata et al. (2007) PNAS 104, 11921.

## 3S1-3 Understanding the Multiscale Dynamics of Complex Biological Systems from Single Molecule Experiments.

Understanding the Multiscale Dynamics of Complex Biological Systems from Single Molecule Experiments.

*Chun Biu Li(1), Haw Yang(2) and Tamiki Komatsuzaki(1). (1: Molecule & Life Nonlinear Sciences Laboratory Research Institute for Electronic Science (RIES) Hokkaido University; 2:)*

The rapid developments in the single molecule spectroscopy enable us to reveal detailed conformational dynamics of protein in the molecular level that would otherwise be masked in ensemble measurements. Recently we have established a novel data-driven methodology [1] to extract the underlying biological modeling directly from the single molecule experimental time series. The outcomes are the multiscale state-space networks describing the protein conformational dynamics at different timescales with high predictive power. Based on the current innovations of network theory [2], I will present in this talk the potentiality of using the multiscale state-space network as a mathematical platform for the study of diverse aspects of biological phenomena, such as the response from external stimulus, robustness and adaptability of protein functions, etc. We expect that our methodology can lead to new insights into biomedical applications, such as drug discovery, when prediction and controlling tasks are performed based on time series data.References:[1] "Multiscale Complex Network of Protein Conformational Fluctuation in Single-molecule Time Series", C.B. Li, H. Yang, T. Komatsuzaki, Proceedings of National Academy of Sciences USA, Vol. 15, pp536 (2008).[2] "Network Biology: Understanding the Cell's Functional Organization" , A-L. Barabasi, Z.N. Oltvai, Nature Reviews, Vol. 5, pp101 (2004).

## 3S1-4 低分子化合物の抗プリオン活性予測法構築に向けて：アッセイ結果を説明する評価関数の探索

Toward the construction of anti-prion activity prediction method for small compounds: modeling of evaluation scheme from assay results

*Hironori K. Nakamura. (Division of Prion Research, Center for Emerging Infectious Diseases, Gifu University)*

Prion diseases such as Creutzfeldt-Jakob disease (CJD) in human and bovine spongiform encephalopathy (BSE) in cow are infectious fatal neurodegenerative diseases, and there is no efficient treatment at this stage. These are caused by transformation of prion protein from normal cellar form to abnormal scrapie form. It is the important issue how we can find drug-candidate compounds for these diseases efficiently. Our group previously found a new anti-prion compound, GN8 with $IC_{50}$=1μM, by *in silico* screening [1]. After the discovery, we further conducted *in silico* screening to obtain anti-prion drug candidates, using AutoDock and ZINC compound database. We evaluated the anti-prion activity of selected compounds using the cell line model. Consequently, we obtained lots of compounds with a variety of anti-prion activity, and four compounds had particularly high anti-prion activity among two hundreds compounds [2].

シンポジウム