【セミナー報告】

セミナー報告

1. " Volitional control of neural activity: implications for brain-computer interfaces."

Eberhard E. Fetz (Dept. of Physiology and Biophysics, Washington National Primate Research Center, University of Washington, Seattle WA, USA)

(2004.4.8)

The activity of many cortical neurons is modulated by appropriate sensory stimulation and/or during performance of behavioral tasks. In addition to these well-known sources of drive there appears to be an unappreciated additional modality that arises from internally generated activity and is under "volitional" control. This volitional drive appears in experiments in which monkeys were operantly trained to control the activity of cortical neurons with biofeedback. It also appears in more recent brain-computer interface studies in which monkeys controlled the position of cursors or robotic arms with cortical activity under closed-loop conditions. This talk will review evidence from these and other studies that suggest a volitional modality for cortical neurons, and will speculate on the implications for implantable brain-computer interfaces.

（担当：関　和彦）

2. Signaling through ion channels: from molecules to behavior

Dr. Paul Slesinger (Assistant Professor, Peptide Biology Laboratory, Salk Institute for Biological Studies, USA)

(2004.5.19)

Part 1. GIRK channels are activated by different combinations of Gbg subunits in vitro but only couple to pertussis toxin (PTX) - sensitive G proteins in vivo. The molecular interactions underlying the formation of these distinct signaling pathways are not well understood. I will present evidence that the C-terminal domain of the GIRK channel plays a central role in organizing a PTX-sensitive G protein signaling complex. These results suggest that GIRK channels exist in a G protein signaling complex that may be specified by Gbg (i/o) binding to the C-terminal domain of GIRK channels. This region implicated in G binding overlaps with a segment in IRK1 channels involved in Andersen's disease, suggesting a possible mechanism for how Gbg subunits may alter channel gating. (Ref.: J. Physiol. (2004) 555, 643-657)

Part 2. The rewarding effect for drugs of abuse is mediated by activation of the mesolimbic dopamine (DA) system while putative anti-craving compounds inhibit the system. Interestingly, different GABABR agonists can exert similarly opposing effects on reward, but the cellular mechanisms involved are unknown. We found that the coupling efficacy (EC50) of GABABR to G protein-gated inwardly rectifying potassium (GIRK) currents was much lower in DA-neurons than in GABA-neurons of the ventral tegmental area (VTA). I will discuss these new findings within the context of drug addiction and G protein regulation of GIRK channels. (Ref.: Nature Neurosci. (2004) 7, 153-159)

（担当：久保　義弘）

3. Cell volume sensitive ion channels in the regulation of erythrocyte apoptotic cell death
（赤血球のアポトーシスと細胞容積感受性イオンチャネル）

Florian LANG (Department for Physiology, University of Tubingen, Germany)

(2004.5.25)

Cells entering programmed cell death or apoptosis destroy their genetic information by DNA degradation and expose phosphatidylserine to the outer leaflet of the cell membrane. Phosphatidylserine exposing cells are recognized by macrophages, which bind those cells engulf and degrade them.

Erythrocytes are devoid of DNA and have hitherto been considered not to undergo apoptosis. However, profound osmotic erythrocyte shrinkage, oxidative stress, energy depletion or lack of Cl^- activate a Ca^{2+} permeable unspecific cation channel with subsequent stimulation of a Ca^{2+} sensitive scramblase which leads to phosphatidylserine exposure at the cell surface. Ca^{2+} further activates the GARDOS K^+ channels leading to cellular loss of K^+, subsequent cell shrinkage and further activation of the cation channels and scramblase. Pharmacological inhibition of the cell volume regulatory cation channel or absence of extracellular Ca^{2+} blunts but does not abolish osmotically induced erythrocyte apoptosis pointing to the involvement of additional proapoptotic mechanisms.

Compelling evidence points to a role of premature apoptosis in the pathophysiology of several forms of anemia. Moreover, activation of cell volume regulatory cation channels may be important during infection of erythrocytes with Plasmodium falciparum, which imposes oxidative stress on the host cell membrane and thus activates several channels including the cation channel. Subsequent host cell apoptosis presumably accelerates the in vivo removal of the infected cell.

（担当：岡田　泰伸）

4. Zebrafish 行動異常 mutant にみるシナプスの形成と機能

Fumihito Ono (University of Florida, USA)

(2004.7.2)

我々は，ドイツで Large scale screening によって単離されてきた行動異常をしめすゼブラフィッシュの mutant を，遺伝学的手法でなく生理学的に解析していくことによって，channel や receptor の働きに関する新しい知見がえられないかと研究を始めた。行動異常といっても記憶などの高度の機能ではなくて，まったく体が動かなかったり筋無力症状をしめしたりという，障害部位としては運動神経より末梢側が想定される mutant である。その結果，rapsyn とよばれる ACh receptor (AChR) の神経筋接合部への集積にかかわる分子の mutant，AChR の 1 サブユニットの折りたたみの障害により膜上に AChR を全く発現しない mutant，receptor の点変異により ACh 電流の減衰がいちじるしく遅くなる mutant などを同定した。これらの mutant から得られた，AChR や rapsyn の新しい役割に関する知見や，以上の結果の延長としての今後の研究方向も含めてお話しする。

（担当：岡村　康司）

5. いわゆる primary evoked response について－脳磁図によるアプローチ（は可能か？）

乾　幸二（生理研　感覚運動調節研究部門）

(2004.7.21)

脳磁図を用いて触覚，痛覚，聴覚，視覚のそれぞれの刺激対する皮質活動時間経過を詳細に検討したところ，以下のような共通点が見いだされた。1) 活動の主な流れは一定方向であり，近接する部位が順次活動する。2) あ

る部位の興奮が次の部位へ伝えられる潜時は概ね 5 ミリ秒である。3) おおよそ刺激後 50 ミリ秒以内に生じる活動は全て，10 ミリ秒間隔で活動の向きを 2 回逆転させる 3 相構造を示す。従って共通する層間伝導様式があるものと考えられる。4) 遅い潜時に開始する活動はこの 3 相構造を持たず経過が長い（100 ミリ秒前後）。この成分は刺激頻度や注意の影響を顕著に受ける。従って 3) とは異なる発生メカニズム，異なる機能を有すると考えられる。3) は動物の脳表面から記録される初期誘発電位，いわゆる primary evoked response に相当すると考えられる。同一皮質部位で向きの異なる双極子が形成されるためには，異なる皮質層での異なる sink-source パターンが必要である。current source density analysis (CSD) の手法を用いた最近の動物での研究は，初期第 4 層の活動とそれに続く 1-2 層の活動が feedforward pathway の活動様式の基本であることを明らかにしており，脳磁図で観察された 3 相構造を持つ初期活動は，順次信号を伝える feedforward pathway の複数層の活動を反映するものと考えられる。

（担当：達本　徹）

6. 二光子励起イメージング法を用いたグリア・脳内血流機能の観察の試み

平瀬　肇（理化学研究所・平瀬ユニット・ユニットリーダー）

(2004.8.2)

I would like to introduce our approaches to investigate neuron-glia-blood flow couplings using the in vivo two-photon microscopy technique. First, I will present our recent work on spontaneous calcium events among astrocytes in the neocortex (Hirase et al., PLoS Biology, 2003 --- www.plosbiology.org). In the second part of the talk, I would like to introduce capillary level circulation imaging in the neocortex in epileptic foci (Hirase et al., Neuroscience, in press). Abstracts of the two studies were pasted as below respectively.

Large and long-lasting cytosolic calcium surges in astrocytes have been described in cultured cells and acute slice preparations. The mechanisms that give rise to these calcium events have been extensively studied in vitro. However, their existence and functions in the intact brain are unknown. We have topically applied Fluo-4 AM on the cerebral cortex of anesthetized rats, and imaged cytosolic calcium fluctuation in astrocyte populations of superficial cortical layers in vivo, using two-photon laser scanning microscopy. Spontaneous $[Ca^{2+}]i$ events in individual astrocytes were similar to those observed in vitro. Coordination of $[Ca^{2+}]i$ events among astrocytes was indicated by the broad crosscorrelograms. Increased neuronal discharge was associated with increased astrocytic $[Ca^{2+}]i$ activity in individual cells and a robust coordination of $[Ca^{2+}]i$ signals in neighboring astrocytes. These findings indicate potential neuron-glia communication in the intact brain.

Local hemodynamics of cerebral cortex is the basis of modern functional imaging techniques, such as fMRI and PET. Despite the importance of local regulation of the blood flow, capillary level quantification of cerebral blood flow has been limited by the spatial resolution of functional imaging techniques and the depth penetration of conventional optical microscopy. Two-photon laser scanning microscopic imaging technique has the necessary spatial resolution and can image capillaries in the depth of the cortex. We have loaded the serum with fluorescein isothiocyanate (FITC) dextran and quantified the flow of red blood cells (RBCs) in capillaries in layer 2/3 of the mouse somatosensory cortex in vivo. Basal capillary flux was quantified as ~28.9+- 13.6 RBCs/sec (n= 50, mean+-std) under ketamine-xylazine anesthesia and 26.7 +-16.0 RBCs/sec (n=31) under urethane anesthesia. Focal interictal (epileptiform) activity was induced by local infusion of bicuculline methchloride in the cortex. We have observed that capillary blood flow increased as the cortical local field events developed into epileptiform in the vicinity of GABA receptor blockade (<300 micro meters from the administration site). Local blood flow in the interictal focus increased significantly (42.5+-18.5RBCs/sec, n=52) relative to the control conditions or to blood flow measured in capillaries at distant (>1mm from the focus) sites from the epileptic focus (27.8+-12.9 RBCs/sec, n=30). These results show that hyper-synchronized neural activity is associated with

increased capillary perfusion in a localized cortical area. This volume is significantly smaller than the currently available resolution of the fMRI signal.

（担当：河西　春郎）

7. Oligodendrogenesis in Development and Disease

Bruce D.Trapp (The Lerner Research Institute The Cleveland Clinic Foundation:USA)

(2004.8.27)

This seminar will review data from the Trapp lab that characterizes oligodendrocyte production in developing rodent brain and in demyelinated lesions in the brain of individuals with Multiple Sclerosis (MS). In the developing rodent brain, oligodendrocytes appear in a temporal and spatial sequence that preceeds myelination by several days. These cells, referred to as pre-myelinating oligodendrocytes (PMO), symmetrically extend multiple, myelin protein-positive processes. They are generated from oligodendrocyte progenitor cells (OPC's) that express the sulfated proteoglycan NG2. PMO's have a limited lifespan and either myelinate axons or die by apoptosis. As they begin to myelinate, PMO polarize their surface membranes and target proteins to distinct membrane domains. After oligodendrocyte production is complete, the NG2-positive OPC's remain as an abundant cell type in the mammalian CNS. Multiple Sclerosis (MS) is an inflammatory demyelinating disease of the CNS. While some MS lesions can be remyelinated early in the disease process, most chronic MS lesions are not remyelinated. Remyelination requires generation of new oligodendrocytes. We investigated chronic MS lesions to determine if the failure of remyelination was due to absence of progenitors, failure of progenitors to produce new oligodendrocytes or failure of new oligodendrocytes to myelinate. We detected both oligodendrocyte progenitor cells and pre-myelinating oligodendrocytes in chronic MS lesions. The oligodendrocytes expressed myelin proteins but failed to remyelinate axons. They did, however, extend processes that associated with axons. Failure of remyelination in MS is due in part to lack of oligodendrocyte-axon interactions that induce the transition of the oligodendrocyte from a non-polarized to a polarized epithelial cell.

（担当：池中　一裕）

8. Transmitter effects on GIRK channels and on constitutively active KirNB channels in brain neurons.

Professor Yasuko Nakajima (Department of Anatomy and Cell Biology, University of Illinois at Chicago, College of Medicine)

(2004.8.27)

中島重広教授・泰子教授ご夫妻は，これまで，イオンチャネル機能調節の分子機構と，神経系における生理的意義について連綿と研究を進めてこられました。近年は，特に，G 蛋白質結合型内向き整流性 K^+ チャネルを対象として，優れた研究成果を多数発表されていらっしゃいます。今回，国際解剖学会ご出席のため来日される機会を活かし，上記のセミナーをお願いいたしました。

（担当：久保　義弘）

9. Mechanisms of GIRK (Kir3) channel inhibition by transmitters

Professor Shigehiro Nakajima (Department of Pharmacology, University of Illinois at Chicago, College of Medicine)

(2004.8.27)

中島重広教授・泰子教授ご夫妻は，これまで，イオンチャネル機能調節の分子機構と，神経系における生理的

意義について連綿と研究を進めてこられました。近年は，特に，G 蛋白質結合型内向き整流性 K^+ チャネルを対象として，優れた研究成果を多数発表されていらっしゃいます。今回，国際解剖学会ご出席のため来日される機会を活かし，上記のセミナーをお願いいたしました。

（担当：久保　義弘）

10. Synfire Chains and Cortical Songs: Temporal Modules of Cortical Activity

Yuji Ikegaya (Department of Biological Sciences, Columbia University)

(2004.8.27)

How can neural activity propagate through cortical networks built with weak, stochastic synapses? We find precise repetitions of spontaneous patterns of synaptic inputs in neocortical neurons in vivo and in vitro. These patterns repeat after minutes, maintaining millisecond accuracy. Calcium imaging of slices reveals reactivation of sequences of cells during the occurrence of repeated intracellular synaptic patterns. The spontaneous activity drifts with time, engaging different cells. Sequences of active neurons have distinct spatial structures and are repeated in the same order over tens of seconds, revealing modular temporal dynamics. Higher order sequences are replayed with compressed timing.

（担当：窪田　芳之）

11. Axon-glia interactions at the node of Ranvier

Elior Peles (The Weizmann Institute of Science: Israel)

(2004.9.6)

Efficient and rapid propagation of action potentials in myelinated axons depends on the molecular specialization of the nodes of Ranvier and particularly, on the clustering of Na^+ channels at the nodes, which forms the molecular basis for saltatory. The nodal region is organized into several distinct domains, each of which contains a unique set of ion channels, cell adhesion molecules and cytoplasmic adaptor proteins. This organization is essential for the rapid propagation of action potentials and its disruption results in pathophysiological changes often seen in demyelinating diseases. The local differentiation of myelinated axons is tightly regulated by oligodendrocytes and myelinating Schwann cells. Two cell recognition molecules, Caspr and Caspr2 mediate axoglial interactions around the nodes and play an important role in the organization of the nodal environs by two different mechanisms: Caspr and its associated protein contactin, participate in the generation of a barrier-like structure at the paranodal junction formed at both sides of the nodes, whereas Caspr2 associates with the contactin related TAG-1 and serves as a scaffold that maintains K^+ channels at the nearby juxtaparanodal region. At the nodal axolemma Na^+ channels are localized and associate with two cell adhesion molecules of the immunoglobulin superfamily, NrCAM and Neurofascin-186 (NF186), as well as the cytoskeletal adaptor ankyrin G and the actin-binding protein spectrin βIV. Using an expression cloning strategy, we have recently identified a novel glial receptor for the nodal CAMs. This protein, termed Gliomedin, mediates axoglial interaction in PNS nodes and may play a role in the formation and maintenance of Na+ channel clustering at this site.

（担当：池中　一裕）

12. A novel GABAergic afferent system selectively controls thalamocortical cells in higher-order thalamic nuclei.

(1) Dr. Hajnalka Bokor (Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary)

(2004.9.13)

In contrast to the exceedingly diverse cortical inhibitory networks, thalamus is characterized by a more simple GABAergic system dominated by afferents arising from the thalamic reticular nucleus (nRt). Here we describe a conceptually new type of GABAergic afferent pathway, distinct from nRt, that exerts powerful inhibitory effect selectively in higher order thalamic relays. Large GABAergic terminals formed by axons originating in the anterior pretectal nucleus (APT) selectively innervated the proximal dendrites of relay cells via multiple release sites. Stimulation of APT afferents revealed a GABAA - receptor mediated, monosynaptic IPSC in thalamocortical cells in vitro and exerted pronounced inhibitory influence on relay cell activity in vivo. Juxtacellular recording and labeling in vivo disclosed APT neurons with firing properties phase-locked with or independent of EEG activity and justified the APT-thalamic pathway at the single cell level. Our data demonstrate a novel GABAergic component in thalamocortical networks that exert powerful and complex control on relay cells involved in higher order functions.

（担当：窪田　芳之）

13. Unprecedented target selectivity of endocannabinoid signaling and perisomatic inhibition in layer V of the somatosensory cortex

(2) Dr. Istvan Katona (Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary)

(2004.9.13)

Retrograde synaptic signaling mediated by endocannabinoids plays a major role in controlling synaptic transmission between interneurons and principal neurons throughout the brain. We combined high-resolution anatomical analysis of CB1 receptor distribution with electrophysiological recordings to examine if there is a pattern in endocannabinoid signaling at distinct synapses of the somatosensory cortex or alternatively, all principal neuron types are able to control its own GABAeric input. Immunostaining for CB1 receptors in the rat somatosensory cortex revealed a striking layer-specific axonal and somatic labeling with highest densities in layers II and VI. Electron microscopic investigations showed that all CB1-positive boutons contain GABA and form symmetric synapses. Double-immunostaining for several neurochemical markers revealed that only large cholecystokinin-positive cells (57%) and calbindin-immunoreactive neurons (33%) express CB1 receptors. Since cholecystokinin and calbindin labeled different neuronal populations, CB1 receptor-positive cells form two morphologically and neurochemically distinct populations in the rat somatosensory cortex. Finally, we found that endocannabinoid-sensitive GABAergic input from these two types of interneurons shows a striking postsynaptic selectivity. Although GABAergic IPSCs in a population of pyramidal cells in layer V and all pyramidal cells in layers II-III was regulated by cannabinoids and could undergo depolarization-induced suppression (DSI), we found an unprecedented population of pyramidal neurons in layer V, which did not receive perisomatic inhibition from cannabinoid-sensitive GABAergic axon terminals and could not undergo DSI. Thus, endocannabinoid signaling in the neocortex shows a striking synapse specificity depending on the identity of both the pre- and the postsynaptic element of the synapse.

（担当：窪田　芳之）

14. From Peppers to Peppermints: An Emerging Molecular Logic of Thermosensation

Dr. David Julius (University of California, San Francisco)

(2004.9.24)

We are interested in determining the molecular basis of somatosensation - the process whereby we experience touch and temperature - with an emphasis on identifying molecules that detect noxious (pain-producing) stimuli. We are also interested in understanding how somatosensation is altered in response to tissue or nerve injury. Our approach has been to identify molecular targets for drugs or natural products that mimic psychophysical effects of commonly encountered somatosensory stimuli, such as heat or cold. Using this strategy, we have identified two members of the TRP channel family, TRPV1 and TRPM8, which are activated by capsaicin and heat or menthol and cold, respectively. One of our main interests has been to determine the molecular mechanism(s) by which tissue injury and inflammation produces hypersensitivity of primary afferent neurons to heat (thermal hyperalgesia). We have elucidated two basic mechanisms that contribute to this process: one involving the direct interaction of inflammatory mediators with TRPV1 such that they serve as positive allosteric modulators of this heat-activated channel, and another involving the potentiation of TRPV1 gating downstream of phospholipase C-coupled receptors. Insights into these mechanisms will be discussed. We have also examined the properties of another TRP channel, TRPA1, which we believe will play an interesting and significant role in inflammatory pain. Our recent studies have shown that TRPA1 is a major site of action of mustard oil (allyl isothiocyanate), the main pungent ingredient in wasabi. Mustard oil excites a subpopulation of capsaicin-sensitive, peptidergic trigeminal neurons, consistent with its ability to produce robust neurogenic inflammation. Our in vitro studies further suggest that TRPA1 functions as a receptor-operated channel, depolarizing sensory neurons in response to pro-algesic agents (such as bradykinin or ATP) that activate PLC-coupled receptors. These findings have significant implications for understanding mechanisms of inflammatory pain and identifying potential therapeutic targets.

（担当：富永　真琴）

15. 膜電位の光学的測定法による心臓興奮伝播パターンのマッピング

酒井　哲郎（琉球大学医学部生理学第二分野）

(2004.9.29)

膜電位の光学的測定法は，膜電位感受性色素により細胞を生体染色し，細胞の膜電位活動を光学的（吸光/蛍光）シグナルとして検出する測定技術である。この測定法には (1) 細胞内微小電極・パッチ電極の摘要が困難な微小・脆弱な細胞,（あるいは細胞の突起部）の膜電位変化の記録が可能であり，さらに，(2) 標本の多数の部位/細胞からの膜電位変化の同時記録が可能である，という二つの大きな特徴がある。ここでは，この実験法の紹介とともに，われわれがおこなっているラット摘出右心房標本を用いた興奮伝播パターンのマッピングの最近の実験結果を紹介したい。

（担当：岡田　泰伸）

16. Real time dynamics of antigen-engaged B cells and interactions with helper T cells in lymph nodes

岡田 峯陽 (Postdoctoral fellow, Dept Microbiology & Immunology, UCSF/HHMI)

(2004.10.18)

Interactions between B and T cells are essential for most antibody responses but the dynamics of these interactions are

poorly understood. By two-photon microscopy of intact lymph nodes, we have been studying real time migration of antigen-engaged B cells and dynamics of their interactions with helper T cells. In this seminar I would like to talk about the studies showing many movies of cell migration in lymph nodes to conclude that antigen-engaged B cells undergo directional migration to the T-zone and form motile conjugates with helper T cells.

（担当：井本　敬二）

17. Phasic inhibition of cortical neurons by acetylcholine

Allan Gulledge (Division of Neuroscience John Curtin School of Medical Research, Australian National University)

(2004.11.1)

Cortical muscarinic acetylcholine receptor (mAChRs) activation is considered important for learning and memory. While the excitatory actions of acetylcholine (ACh) on cortical pyramidal neurons is well characterized, less is known about how phasic applications of ACh may influence information processing in the cortex. We use focal and transient application of acetylcholine (ACh) and carbachol to demonstrate that in neocortical pyramidal neurons phasic mAChR activation produces a delayed hyperpolarising response from rest. These hyperpolarising responses are associated with an increase in membrane conductance due to transient activation of SK-type calcium-activated potassium channels. Importantly, phasic mAChR activation inhibits cortical neurons even in the presence of spontaneous activity induced by tonic mAChR stimulation with bath-applied carbachol. These findings suggest that the phasic bursting of cholinergic neurons may provide a transient inhibitory input to the neocortex while slower, Ach release may create a more general increase in neuronal excitability.

（担当：川口　泰雄）

18. A short history of caged compounds-using light to stimulate rapid cellular chemical reactions

Graham C.R. Ellis-Davies（Drexel University, Philadelphia, USA）

(2004.11.2)

Fox Talbot announced the flash photolysis method to the Royal Society, with a public demonstration of the technique in 1851. Since then, bursts of light have been used by scientists to record and manipulate our reality, culminating in the Nobel Prize awarded to Norrish, Porter and Eigen in 1967. Caged compounds where invented in 1977, and since that time have been used by many physiologists and cell biologists to stimulate biochemical reactions in living cells. This lecture will give a short history of this technique, and will present our latest applications.

（担当：河西　春郎）

19. 「気道上皮表面液層におけるヌクレオチド放出の意義」 “Nucleotide release contributes to airway surface liquid homeostasis”

岡田　聖子 (Cystic Fibrosis/Pulmonary Research and Treatment Center, University of North Carolina at Chapel Hill)

(2004.11.5)

気道上皮表面液層において, ATP 及びその代謝物質は, 受容体を介し, 線毛運動および粘液分泌を促進する。ATP は恒常的にまた刺激に応じて放出され，細胞表面の水解酵素によって迅速に分解され，この迅速な濃度調節が局所ホルモンとしての機能を可能とする。気道上皮表面における ATP 及びその代謝物質の濃度と生理学的意義に

ついて，我々の知見を論ずる。尚，細胞外ヌクレオチドの意義は確立されつつあるが，その放出機構は未だ明らかでない。候補分子のひとつである，voltage-dependent anion channel-1 (VDAC-1) について論ずる。

（担当：岡田　泰伸）

20. Critical Period Mechanisms in Developing Visual Cortex

Dr. Takao K. Hensch（理化学研究所・脳科学総合研究センター　グループ　ディレクター）

(2004.11.16)

Neuronal circuits across several systems display remarkable plasticity to sensory input during postnatal development. Experience-dependent refinements are often restricted to well-defined critical periods in early life, but how these are established remains mostly unknown. A representative example is the loss of responsiveness in neocortex to an eye deprived of vision. We show that the potential for plasticity is retained throughout life until an inhibitory threshold is attained. In mice lacking an isoform of GABA synthetic enzyme (GAD65), as well as in immature wild-type animals before the onset of their natural critical period, benzodiazepines, enhancer of GABA mediated inhibitory transmission through acting to a specific $GABA_A$ receptor, selectively reduced a prolonged discharge phenotype to unmask plasticity. Enhancing GABA-mediated transmission early in life rendered mutant animals insensitive to monocular deprivation as adults, similar to normal wild-type mice. To examine whether a particular inhibitory network controls expression of the critical period, we use a mouse knock-in mutation to α subunits that renders individual $GABA_A$ receptor insensitive to diazepam. Only α1-containing circuits were found to drive cortical plasticity, but α2-enriched connections separately regulated neuronal firing. It is known that $GABA_A$ receptor α1 subunits are preferentially enriched at synapses receiving input from parvalbumin (PV) positivie large basket-cell terminals. Moreover, we show that impaired ocular dominance plasticity by gene-targeted removal of Kv3.1 contributing to PV-cell fast-spiking behaviour directly mimics the GAD65 knockout mouse phenotype in a cell-type specific manner. These results suggest that a threshold level of inhibition within the visual cortex trigger an experience-dependent critical period for a specific $GABA_A$ circuit consolidation.

（担当：窪田　芳之）

21. A Hidden history of synapse

辻　繁（元フランス CNRS　主任研究員，Departement de cytology, University, School of Medicine, USA）

(2004.11.19)

22. Representation of self-motion by cortical and subcortical neurons.

Dora Angelaki (Department of Anatomy and Neurobiology, Washington University, School of Medicine, USA)

(2004.11.19)

我々が自分あるいは周囲の運動の知覚には，視覚入力と前庭入力が相互に影響しあう。これまで回転運動を用いた研究が行われてきたが，直線運動についての報告は少なかった。直線運動の認知には，回転運動とは異なり，被験者の注視点の位置などの様々な要素が影響する。そこで直線運動の知覚に際して視覚入力と前庭入力がどのように脳内で統合され，運動として認知されるかについて，サルを用いた行動学的実験，単一ニューロン活動記録，モデルによる検討などについて，話して頂いた。

（担当：南部篤，伊佐　正）

23. 3 種類の SNARE 蛋白質阻害の伝達物質放出速度への影響

坂場 武史（Max-Planck 生物物理化学研究所）

(2004.12.27)

SNARE 蛋白質 (Synaptobrevin, SNAP-25, Syntaxin) は細胞における膜融合を制御ないし調節すると考えられており，生化学，細胞生物学的なアプローチを用いた研究が盛んに行われている。また，SNARE 蛋白質の機能を阻害する毒素はシナプス伝達をほぼ完全に阻害するので，これらの蛋白は伝達物質放出に重要な役割を果たしていると考えられている。一方で，伝達物質放出の kinetics, Ca 感受性などにどのように影響を与えるかは不明の点が多い。そこで，神経終末 (calyx of Held) にパッチ電極を介して毒素ないしペプチドを注入し，シナプス終末への Ca 流入ないし Ca-uncaging により誘発される伝達物質放出が阻害される過程で，放出の kinetics がどのように変化するかを調べた（Stein/Jahn のグループとの共同研究）。

（担当：井本　敬二）

24. Prostaglandin D synthase expressed in glia is involved in spatial learning

江口　直美（(財）大阪バイオサイエンス研究所・分子行動生物学部門，早稲田大学客員教授）

(2005.1.14)

（担当：重本　隆一）

25. Reciprocal control between the prefrontal cortex and the raphe nuclei. Role of serotonin receptors

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(2005.1.18)

The prefrontal cortex (PFC) is the most anterior portion of the frontal lobes and controls high-level brain functions such as cognition. In the mammalian brain the serotonergic system (which originates in the raphe nuclei) innervates the PFC and modulates its activity. Although the exact role of serotonergic neurotransmission in the PFC remains largely unknown, the PFC of the rodent and primate brain express serotonin 5-HT2A (excitatory) and 5-HT1A (inhibitory) receptor subtypes abundantly. As pharmacological evidences involve the PFC and the serotonergic system in severe psychiatric disorders, the main goal of our research has been to study the circuit between these structures in rodents at a physiological and neurochemical level. Our first results describe the complex regulation of serotonergic neuron activity by the PFC. We have demonstrated that the pharmacological activation of 5-HT1A and 5-HT2A receptors of the PFC markedly affects serotonergic transmission in terms of 5-HT activity and release. Conflicting results have been reported for the cellular localization of 5-HT2A receptors responsible for the excitatory effects of 5-HT in the PFC. Our experiments reveal that the excitatory effects of 5-HT2A receptor activation are unrelated to thalamocortical terminals and suggest a main localization in pyramidal neurons. Moreover, double in situ experiments report a large co-expression of 5-HT1A and 5-HT2A receptors in the same pyramidal neurons of the PFC. We have showed that the activation of these receptors by 5-HT exert opposite effects on pyramidal activity. However, the different segregation of 5-HT1A (axon hillock) and 5-HT2A (apical dendrites) receptors within the same pyramidal neuron could explain the overall inhibitory effect of 5-HT in the PFC.

（担当：窪田　芳之）

26. 生体内凍結技法による“生きた動物臓器”の免疫組織化学的解析

大野　伸一（山梨大学解剖学第 1）

(2005.1.27)

近年細胞生物学分野での形態学的解析法の進歩は顕著であり,遺伝子工学的手法や免疫細胞化学法を併用し,生きた細胞内での特定蛋白質の合成や細胞内輸送等が明らかにされてきた。さらに細胞膜や細胞小器官等への特定蛋白質の局在が，光顕レベルで直接可視化もできるようになった。しかし一般的な光顕および電顕形態学的研究の試料作製法では,細胞組織の浸漬あるいは灌流固定,脱水，包埋，薄切，染色（色素や重金属）が必須であり，このような試料処理過程においては，形態学的変化が起こることが良く知られている。これらの形態学的変化を出来るだけ避けるために，特に電顕用観察には，切除した新鮮無固定生物試料を速やかに急速凍結し，凍結置換固定法や凍結割断エッチング法による超薄切片やレプリカ膜で検討することも行われてきた。最近では加圧凍結法も普及してきており，凍結良好な細胞組織の範囲が飛躍的に拡大し，今後ますます細胞組織の生体内構造と機能を明らかにしようとする研究が盛んになると思われる。

しかし実験動物の臓器によっては，脳や腎臓に代表されるように生体内において循環血流の影響を強く受けていて，急速凍結するために組織試料を生体内から切り離すことによる形態変化が避けられないことが考えられた。すでに独自に開発した生体内凍結技法により，マウス脳や腎臓を直接生体内で凍結して微細構造を解析したが，従来の切除組織での急速凍結試料による微細構造とは異なることが明らかにされた。このような形態学的相違は，試料切除時に循環血流が遮断されて，血管内圧の極端な低下と酸素欠乏によるためと考えられた。従って生きた動物の脳や腎臓等の新鮮無固定試料を急速凍結しても，真の生体内微細構造を検索することにはならないことが明らかとなった。そこで 21 世紀の形態学的アプローチとして，生体内において生理的機能に対応した形態変化を明らかにするために，生体内凍結技法が有用であることをマウス各種臓器を例として報告する。さらにこの生体内凍結技法は，種々の機能状態下での“生きた動物臓器”の形態学的解析以外に，その特定蛋白分子局在の免疫組織化学的解析にも有効であることを示す。

（担当：重本　隆一）

27. Getting published in Nature Neuroscience: myths and facts about the editorial process.

I-Han Chou (Associative Editor of Nature Neuroscience)

(2005.2.1)

Nature Neuroscience is the highest impact primary research journal in neuroscience. We are a multidisciplinary journal, publishing papers in all areas of neuroscience, including molecular, cellular, systems and cognitive neuroscience, as well as psychophysics, computational modeling and diseases of the nervous system. We are highly selective, publishing only the small fraction of our submissions that are of the highest quality and significance. I will present an overview of our editorial process, from selecting papers for review to final decision, and talk about effective strategies used by successful authors.

（担当：宮田　麻理子）

28. Functional architecture, oblique effect and feedback influence to areas 17 and 18 in the cat's visual cortex

Tiande Shou (Vision Research Laboratory, Center for Brain Sci. Res., Fudan University, Shanghai, China)

(2005.2.4)

Using intrinsic signal optical imaging and electrophysiological single unit recording methods neurons in cortical area 21a in the cat's visual pathway, which is corresponding to V4 in the monkey, were found to be organized in a columnar manner according to similarity of their orientation preference like neurons in areas 17 and 18. This functional architecture provided a neural basis of psychological "oblique effect", which is a phenomenon showing that visual ability in horizontal and vertical meridians is better than that in oblique meridians.

The overall feedback effect of higher-order area 21a on lower-order areas 17 and 18 was found to be excitatory and spatial frequency-dependent when measured with inactivating of area 21a by GABA or lesion by liquid nitrogen.

（担当：小松　英彦）

29. Humour and the Brain

Prof.Vinod Goel (Dept.of Psychology, York University)

(2005.2.7)

Humour, a unique human characteristic, plays a critical role in thought, communication and social interaction. Successful jokes involve a cognitive juxtaposition of mental sets, resulting in surprise, followed by an affective feeling of amusement. The element of surprise, often derives from the fact that the alternative interpretation/resolution offered by the punchline of a joke is physically or socially forbidden. When I tell you a joke, you may respond in one of several ways. You may (i) not get the joke; (ii) get the joke and find it funny; (iii) get the joke and not find it funny because you have heard it before; (iv) get the joke and not find it funny because it offends you. I will discuss several fMRI studies that explore the functional neuroanatomy of each of those possibilities.

（担当：本田　学）

30. 単一細胞または単一シナプスの特性から神経細胞集団またはシナプス集団の性質を予測する理論的方法

加藤　英之（ニューヨーク大学　研究員）

(2005.2.17)

単一神経細胞および単一シナプスの動態が精密に特徴付けられてきたが，脳の機能は一般に，細胞集団，シナプス集団といった巨視的レベルで，実現されると考えられるため，微視的性質から巨視的性質への演繹する手法が重要となる。そのような手法として有用な Fokker-Planck の方法を直感的に説明し，これよる，1) 細胞集団の同期的発火状態の解析，2) 単一細胞上にある多数のシナプスがスパイクタイミング依存可塑性で変化する様子の解析，さらにこの考え方に基づいて，細胞集団の膜電位状態を細胞外測定から予測する手法を紹介する。

（担当：宮田　麻理子）

31. Tangential Migration of Cortical Interneuron

Guillermina Lopez-Bendito (CSIC & Universidad Miguel Hernandez, Alicante, Spain)

(2005.2.21)

One of the most remarkable recent discoveries in developmental neuroscience is related to the observation that a substantial fraction of GABAergic cortical interneurons originates outside of the cerebral cortex and migrate tangentially to their final location within the cortical layers. Both repulsive and attractive cues seem to be involved in the regulation of cortical interneuron migration from ventral to dorsal areas of the telencephalon (Marin and Rubenstein, 2001; 2003). Furthermore, the guidance of these interneurons may also be influenced by neuronal activity. Indeed, several studies have described the early expression of GABA and glutamate receptors at the cerebral cortex before the formation of synapses (Metin et al., 2000; Lopez-Bendito et al., 2002a; 2002b; 2005). Some of these receptors can be activated in vitro by specific agonist, indicating that the may be also activated in vivo by their natural ligands, also expressed at this early stages. For example, the metabotropic receptor for GABA, $GABA_B$, is highly expressed by tangential migrating interneurons going to the cortex, and its blockade in vitro leads to a derailment of GABAergic interneurons within the neocortex (Lopez-Bendito et al., 2003).

Furthermore, stimulation of AMPA receptors in slice cultures induces neurite retraction and GABA release in tangentially migrating cells (Poluch et al. 2001, Poluch & Konig 2002). These and other additional studies suggest that in vivo, the activation of neurotransmitter receptors might be important for the migration of interneurons although the mechanisms controlling and underlying the activation of these receptors are yet unknown.

（担当：重本　隆一）

32. Precision and variability in the localization of neurotransmitter receptors and ion channels on the neuronal surface.

Dr. Rafael Lujan (Universidad de Castilla-La Mancha, Albacete, Spain)

(2005.2.23)

The impact of neurotransmitter receptors and its effector ion channel on synaptic transmission is largely dependent on their spatial distribution and density in the somato-dendritic compartments of central neurons and, in case of ion channels, on the subunit composition of the individual channels, which determines the single channel properties such as unitary conductance, open-time duration, and open probability. At synapses, it is still assumed that neurotransmitter receptors are located facing axon terminals, so they can bind quickly to the neurotransmitter released in the synaptic cleft. However, this stereotyped view of synapses is more complex than previously thought. Neurotransmitter receptors and ion channels can be located at any subcellular compartment, though they are segragated depending on the subtype/subunit and also on the cell type. Therefore, my interest is to understand how synaptic transmission is mediated by neurotransmitter receptors by obtaining detailed qualitative and quantitative data on the distribution of functional glutamate and GABA receptors and its effector ion channels on the surface of central neurons.

（担当：重本　隆一）

33. 分散培養神経回路網における自己組織化された機能的ネットワーク

工藤　卓（産総研 セルエンジニアリング研究部門，JST）

(2005.2.24)

脳から取り出され，分散培養された神経細胞は培養日数を経るに従って神経突起を伸張し，シナプス結合を形成し，複雑な神経回路網を自律的に構成していく。こうして再形成された生体神経回路網は，脳組織に於いてと同様に自発的な電気的活動を呈し，何らかの情報処理を行いうるように見える。他方脳に於いては，ダイナミックに更新される神経細胞間の機能的結合によってグルーピングされた神経細胞群 (functional neuron assembly) の存在が報告され，その協調的活動が脳内における情報の表現に重要な役割を果たしていることが示唆されている。培養皿上に再構成された神経回路網に於いてもこのような機能的細胞集成体が構成されうるならば非常に興味深い。

そこで，培養に於ける自発的神経活動の時空間パターンを解析する系を確立した。胎生ラット海馬神経細胞を 2 次元多点電極を有する培養皿上で培養し，記録された自発的活動電位の時空間パターンがいくつかのパターンにクラスタリングされるか検討した。さらに，神経細胞間の機能的結合を視覚化するために“Connection MapAnalysis”を考案した。これは，相互相関関数を元に観測された神経細胞の全てのペアについて機能的結合の強度を推定し，2 次元マップに表現するものである。

Connection Map に表現された機能的結合のネットワークは，スケール・フリーネットワークの構造をとり，多くの結合を持つ少数の「ハブ的」な神経細胞が存在することを示していた。これらの解析の結果が示すのは，分散培養された神経細胞は，“ランダムでない”，何らかの意味構造をもった，情報処理に適したネットワークを自己組織化によって構成するらしいということである。

（担当：井本　敬二）

34. Tonic inhibitory conductances mediated by $GABA_A$ receptors.

Dr. Alexy Semyanov (RIKEN, RIKEN Brain Science Institute, Unit Leader)

(2005.3.7)

GABA mediates fast inhibition by activating synaptic ionotropic $GABA_A$ receptors. Low extracellular GABA concentrations also generate a tonic current mediated by high-affinity $GABA_A$ receptors. Tonic inhibition occurs in brain slices, neuronal cultures and in vivo. It is developmentally regulated and is modulated by GABA uptake. We have shown that amplitude of tonic current is different in hippocampal interneurons and pyramidal cells. This has an important role in regulating network excitability and information processing. The pharmacological profile of tonic current also differs depending on extracellular GABA concentration which implies different subpopulations of receptors (binding sites of receptors) are involved. Such heterogeneity of $GABA_A$ receptors may not only be the mechanism to extent the dynamic range of tonic current in response to different GABA concentrations, but also serve as a basis for adaptive plasticity. We have discovered that in both normal and epileptic hippocampal slices tonic $GABA_A$ receptor mediated current is similar at low GABA concentrations. However then ambient GABA is increased the magnitude of tonic current in pyramidal cells from epileptic animals was larger.

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（担当：重本　隆一）

35. 神経活動長期抑制による伝達物質放出確率の変化

桂林　秀太郎（Max-Planc, Bayler 大学，JSPS 海外研究員）

(2005.3.16)

神経伝達物質放出機構の活動依存性の伝達物質放出確率の変化について分子背景を含めて，最新の研究についてセミナーを行なった。

（担当：鍋倉　淳一）

36. 精子の運動活性化・走化性機構

吉田　学（東京大学大学院理学系研究科附属臨海実験所・講師）

(2005.3.17)

受精に先立ち，精子は卵より放出される因子によって活性化され，誘引されることが多くの動物で知られている。この卵に対する精子走化性は，多くの動物において種（または属）特異性があることが解っている。つまり精子走化性現象は，特に体外受精を行う生物において，受精の際に精子が同種の卵を選択し，かつ効率的に接近することを助けていると思われ，生物の生殖戦略を探る上でとても興味深い現象である。しかし，精子走化性についての研究はこれまで非常に少なく，精子誘引物質や精子走化性の分子機構といった知見がほとんど得られていなかった。演者らはこの精子走化性現象が顕著にみられる原索動物のカタユウレイボヤ Ciona intestinalis を主に用いて研究を行ってきた。そしてこれまでに，精子活性化と精子走化性は単一の物質で誘起されることを突き止め，その物質が新奇の硫酸化ステロイドであることを明らかとした。今回はこのユウレイボヤの精子走化性機構にスポットを当て，精子誘引物質及び精子活性化・走化性の分子機構についての最近の知見について紹介する。

（担当：岡村　康司）

37. 機械受容チャネル開閉の分子機構

吉村　建二郎（筑波大学大学院生命環境科学研究科構造生物科学専攻）

(2005.3.29)

触覚や聴覚などを担う機械受容は機械受容チャネルによって行われている。バクテリアの機械受容チャネルは細胞膜の張力に応じて開くチャネルである。このチャネル分子には，外力による構造変化を許す緩さがあり，脂質からの力を感じるセンサーがある。

（担当：岡村　康司）