ML-1 Neural mechanism of emotion in the prefrontal cortex, limbic system and nucleus accumbens

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This century is the era of the brain science. Although emotion was one of the most enigmatic mental processes, recent advance in this academic field has enabled us to approach neural basis of emotion. Among various brain regions involved in emotional experience and behaviors, the prefrontal cortex is thought to be important in prediction, evaluation, decision making, etc. The amygdala plays an important role in stimulus-affect association; the hippocampal formation is crucial for episodic memory. The nucleus accumbens integrates not only converging inputs from these areas but also mesolimbic dopamine inputs from the ventral tegmental area to predict reward or aversion, which is essential in emotional behaviors. In this morning lecture, the neural representation of emotional experience and behaviors in these brain regions is described and discussed, mainly based on the recent findings obtained in our laboratory using animals including monkeys, rats and knockout mice.

ML-2 Novel Prostaglandin Probes for Brain Research

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Molecular design to develop a stable biochemical probe for a study of the role of prostacyclin (PGI_2) in the brain led to the discovery of 15*R*-TIC that selectively binds to a novel PGI_2 receptor, IP_2, expressed in the central nervous system (CNS). This artificial prostaglandin with unnatural configuration at C(15) exhibits high binding affinity for the IP_2 receptor in the thalamus (IC_{50} = 32 nM) and weak affinity for the peripheral-type PGI_2 receptor, IP_1, in the NTS (IC_{50} = 1.2 mM). The length of the ω side-chain and the position of the methyl substituent on the aromatic ring strongly influence the binding characteristics. The features of the IP_2 receptor were elucidated by quantitative mapping, specificity studies, and Scatchard analysis, as well as by a study using knockout mice with a tritium-labeled 15*R*-TIC and related radioligands. In order to conduct *in vivo* PET studies, a rapid coupling between methyl iodide and aryltributylstannane has been developed. This has successfully been applied to the synthesis of short-lived 15*R*-[^{11}C]TIC methyl ester. The PET experiments accomplished the imaging of the IP_2 receptor in the brain of living monkeys and humans through intravenous injection. Elimination of the C(15) chirality results in 15-deoxy-TIC with ten-fold higher affinity for IP_2. Neither 15*R*-TIC nor 15-deoxy-TIC inhibit platelets aggregation while PGI_2 derivatives which bind with IP_1 show a very potent inhibitory effect. These artificial CNS-specific ligands, like natural PGI_2, prevent the apoptotic cell death of hippocampal neurons induced under high (50%) oxygen atmosphere and by xanthine and xanthine oxidase or serum deprivation. 15*R*-TIC protects CA1 pyramidal neurons against ischemic damage in gerbils. In addition, we developed two novel cyclopentenone prostaglandins, NEPP10 and NEPP11, with neurotrophic activities. NEPP10 strongly promotes the neurite outgrowth of PC12 cells, DRG neurons, and CAD cells. NEPP11 exhibits dual activities for the promotion of neurite outgrowth and neural protection (prevention of the glutamate-induced death of HT22 cells). NEPP11 also protects the brain against permanent MCA occlusion using mice. Thus the designed TICs and NEPPs have neuronal survival and relating activities both in vitro and in vivo, providing the possibility as a new type of chemotherapeutic agents for applications in neurodegeneration.

ML-3 Amount of Information in Population Coding

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Information is believed to be represented by excitation patterns of a population of neurons in the brain. Neurons fire stochastically, depending on stimuli from the outside as well as mutual interactions within the population. The present talk addresses some informational and mathematical aspects underlying the scheme of population coding. The following is topics to be discussed

1. Orthogonal decomposition of a firing pattern into firing rates, pairwise correlations and higher-order interactions of neural firing in a population.
2. Synchronous firing and higher-order interactions in a population of neurons.
3. Fisher information and encoding/decoding accuracy in a neural field.
4. Algebraic singularities when multiple targets are presented in a neural field, and their resolution by synfiring

References

H.Nakahara and S.Amari, Information-geometric measure for neural spikes, Neural Computation, 14, 2269-2316, 2002
S.Wu, H.Nakahara and S.Amari, Population coding with correlation and an unfaithful model, Neural Computation, 13, 775-797, 2001
S.Wu. S.Amari and H.Nakahara, Population coding and decoding in a neural field: a computational study, Neural Computation, 14, 999-1026, 2002
S.Amari, H.Nakahara, S.Wu and Y.Sakai, Synchronous firing and higher-order interactions in a neuron pool, Neural Computation, 15, 127-142, 2003

ML-4 Regenerating the central nervous system

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It had long been believed that "regeneration" of the injured central nervous system (CNS) is impossible. In CNS, concepts of "regeneration" include 1) regrowth of the disrupted neuronal axons, 2) replenishment of lost neuronal (neural) cells, and 3) recovery of impaired neural functions. To achieve the CNS regeneration, it is important to recaitulate the normal neural developmental process. Roughly speaking, the CNS development is initiated by the induction of the neural stem cells (NSCs) or early progenitor cells. NSCs are multipotential progenitor cells that have self-renewal activities. Because of their characteristics, there is an increasing interest in NSCs and neural progenitor cells from the aspects of both basic developmental biology and therapeutic applications to the damaged brain. Recently developed techniques have made it possible to isolate, culture, and grow pluripotent self-renewing NSCs from both embryonic and adult brains. This basic research is attracting a lot of attention because of the hope that it will lead to regeneration and reconstruction therapy for the damaged CNS.

ML-5 Alzheimer's Disease: Mechanisms and Development of Therapeutic Strategies

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A large body of knowledge indicated that senile plaques are the most characteristic change in Alzheimer's disease (AD). Senile plaques are formed by deposits of β amyloid which is composed of aggregated amyloid β protein (Aβ) derived from amyloid precursor protein (APP). It is suggested that there exists a mechanism of an increase of Aβ production or a decrease of Aβ degradation in AD. As a matter of fact, mutations in familial Alzheimer's disease (FAD) genes such as *APP, presenilin 1* (*PS1*) and *presenilin 2* (*PS2*) result in an increase of Aβ production, particularly of Aβ42. Apolipoprotein E (ApoE), a genetic risk factor, is also involved in Aβ production and/or its clearance. Thus, an inhibition of Aβ production and a facilitation of β amyloid degradation and clearance are thought to delay the clinical onset and progression of AD, and it is possible to cure AD even after an onset of the disease, if it is still at an early phase.

Researchers studied the fine mechanisms of Aβ production and identified enzymes that cleave-out Aβ from APP. Inhibitors of the cleaving enzymes are proven to be effective in ameliorating AD-like conditions of its animal models and are now being applied to humans. Researchers also found an efficient way of clearing β amyloid deposits by the immune system, which was found effective in animal models. However, a clinical trial of the Aβ vaccination was suspended because of its serious side effect. Notably, some patents developed meningoencephalitis probably due to autoimmune mechanisms. Development of safer vaccines is now in competition.

It did not require 20 years for researchers to establish therapeutic strategies for this devastating disease since the discovery of Aβ. Now that AD is becoming a treatable disease, early diagnosis and early treatment will soon become principle. For this reasons, we must establish specific diagnostic measures urgently. Ligands to image senile plaques and biological markers in the fluid are now being sought.

ML-6 Glia-neuron communication and its roles in brain function

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Recent studies on advanced imaging methods, which allow observation of changes in intracellular and extracellular signaling molecules in real time, have demonstrated that glial cells communicate with one another and with neurons primarily through chemical signals. Such intercellular communication requires the release of transmitters and the expression of receptors for the transmitters on glial cells. We have studied dynamic profiles of astrocytes, which ensheathe synaptic junction, by calcium imaging technique and have revealed that many kinds of neurotransmitter receptors for such as glutamate, acetylcholine, monoamines and ATP are expressed on them. Activation of those receptors by t-ACPD, a specific agonist for metabotropic glutamate receptors (mGluR) can induce characteristic oscillatory increase in calcium concentration (one to five waves per minutes). The oscillatory changes can be observed as calcium waves within a single astrocyte and also in astrocyte network. Almost the same calcium waves can be observed in fresh hippocampal slices by activating mGluR. Furthermore the calcium waves in astrocytes are accompanied by the oscillatory activation of neuronal cells locating around the astrocytes. The oscillatory changes in calcium concentration of neuronal cells is blocked by antagonists for ionotropic glutamate receptors, which means the release of glutamate from the astrocytes during their oscillatory activities. We also found that tetanic stimulation on the Schaffer collateral to cause long term potentiation can induce the increase in calcium concentration in the astrocytes located in the synaptic region. The concept of "tripartite synapse" formed among presynaptic neuron, postsynaptic neuron and surrounding astrocyte can be derived from those findings. However, since we know that the calcium signaling can propagate into the other astrocytes using gap junction and also ATP dependent processes, the activities at one synapse may not cease as a local response at a tripartite synapse, but spread widely into surrounding synapses through astrocyte-networks. Our findings demonstrate the possible participation of astrocyte-neuron networks in the brain and its contribution to the synaptic plasticity and the other higher brain function.

ML-7 The molecular mechanism of neuronal death in Parkinson's Disease suggests possible gene therapy

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Parkinson's disease (PD) is an aging-related movement disorder caused by degeneration of the nigro-striatal dopamine (DA) neurons and DA deficiency in the striatum. We and other workers found both increased levels of: neopterin in cerebrospinal fluid (CSF) that is a marker of activated microglia, beta-2 microglobulin (the light chain of MHC-1), proinflammatory cytokines such as TNF-alpha, IL-1beta and IL-6, and apoptosis-related factors such as anti-apoptotic bcl-2 and pro-apoptotic caspases 1 and 3; and decreased levels of neuroprotective neurotrophins such as brain derived-neurotrophic factor (BDNF) or nerve growth factor (NGF), specifically in the nigro-striatal region of postmortem brain and/or in the ventricular or lumber CSF from idiopathic PD patients, or from animal models such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-PD mice or 6-hydroxydopamine (6-OHDA)-PD rats. These data from postmortem brain and animal models support the hypothesis that the process of cell death in the nigro-striatal DA neurons may be apoptosis. Recent discoveries of the causative gene products of familial PD, Parkin that is a ubiquitin ligase (E3), and alpha-synuclein, indicate that failure of the ubiquitin-proteasome system may cause apoptosis. The initial changes in cytokines may be caused by activated microglia, and then cell death in DA neurons may follow by subsequent changes in cytokines and neurotrophins in glias and DA neurons. However, cytokines either promote signals leading to cell death or exert neuroprotective effects. Our recent studies suggest that increased levels of these cytokines from immune-activated glial cells could be due to compensatory and neuroprotective reaction. In the advanced stage of PD, however, increased levels of these pro-apoptotic cytokines and decreased levels of anti-apoptotic neurotrophins may promote the progress of neuronal cell death. Thus the observed changes in cytokines or neurotrophins could be primary causative events or secondary compensatory responses for DA neurons. The gene therapy for PD should aim both at supplementing the decreased striatal DA level by introducing the genes of DA-synthesizing enzymes such as tyrosine hydroxylase, DOPA decarboxylase, and GTP-cyclohydrolase I, and at preventing cell death by introducing genes that block the process of apoptosis such as BDNF, glial cell line-derived neurotrophic factor (GDNF), or Null1.

ML-8 Discovery and functions of semaphorin receptors, neuropilins and plexins, in neuron network formation

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Identification of molecules that guide axons with a high degree of precision is one of major subjects in developmental neurobiology. Over the past decade, a variety of axon guidance molecules with attractive or repulsive natures and their neuronal receptors have been identified.

Semaphorin comprises a family of more than 20 molecules, and functions as repellent or attractant for neurons and regulates axonal growth. On the other hand, neuronal membrane proteins referred to as neuropilin and plexin have been shown to function as semaphorin receptors. Nowadays, 2 neuropilins (neuropilin-1 and neuropilin-2) and more than 10 plexins have been identified.

Here, I will overview on semaphorins and their receptors, in the following 4 points.

1. How were semaphorin receptors, neuropilins and plexins, discovered?
2. How do neuropilins and plexins mediate semaphorin activities?
3. What happen in nerve fiber projection and neuronal cell migration in theSema3A mutant, neuropilin-1 mutant, neuropilin-2 mutant and plexin mutant mice?
4. Finally, on the bases on the findings obtained in vitro and in vivo analyses, I will discuss functions of neuropilin/plexin-mediated semaphorin activities in neuron network formation.