IBRO-TIFR Neuroscience Symposium

Wednesday - February 4, 2015

Lecture Theatre (AG66), TIFR, Mumbai

Tata Institute of Fundamental Research
Homi Bhabha Road, Colaba
Mumbai 400 005, INDIA

PROGRAM

Wednesday - February 4, 2015 Venue : AG66 / AG69

IBRO-TIFR Neuroscience Symposium

9.00	*Opening remarks by **Keiji Tanaka** (Chair, APRC)*
9.10	***Plenary Lecture:*** The Computational Logics of Network in Motion – from Microcircuits to Selection of Behaviour - ***Sten Grillner***
10.00	***Lecture 1:*** What Does Our Visual System Know about the World? - ***S.P. Arun***
10.35	***Lecture 2:*** Developmental Plasticity of Vestibular Circuits Regulates the Behavioral Outcome of Spatial Coding - ***Ying-Shing Chan***
11.10	Coffee Break
11.30	***Lecture 3:*** Functional Division among Prefrontal Areas of Macaque Monkeys - ***Keiji Tanaka***
12.05	***Lecture 4:*** Pathogenesis and Therapy for Alzheimer's Disease (AD) and Parkinson's Disease (PD) - ***Yoo-Hun Suh***
12.40	***Lecture 5:*** Large-scaled Network Reorganization during Recovery from Partial Spinal Cord Injury - ***Tadashi Isa***
13.15	Lunch Break
14.15	***Lecture 6:*** Ischaemia-Induced Neuronal Cell Death is Mediated by Molecular Targeting of CaMKII Phosphorylated at T253 - ***JAP Rostas***
14.50	***Lecture 7:*** The Role of Orexinergic Projections to the Locus Coeruleus Nucleus in Morphine Tolerance and Dependence - ***Saeed Semnanian***
15.25	***Lecture 8:*** Early Adverse Experience and the Development of Psychopathology - ***Vidita A. Vaidya***
16.00	***Colloquium:*** Molecular-motor transport in cells: what is the importance of motor number, and how might this be regulated? - ***Steven Gross***
17.00	High Tea
18.00	***Indian Music Program*** **- Pritam Bhattacharjee**, Indian Classical vocalist from Mewati Gharana **Venue: Homi Bhabha Auditorium Foyer**
20.00	**Banquet Dinner at TIFR**

ABSTRACT: PLENARY LECTURE

The Computational Logics of Network in Motion – from Microcircuits to Selection of Behaviour

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Vertebrates have an astounding ability to coordinate the complex movements required for adaptive behavior utilizing a set of motor programs, like those coordinating eye, head and locomotor movements. These motor programs have been conserved throughout vertebrate phylogeny and we now understand how many of these motor programs are designed at the microcircuit level. Moreover, the neural mechanisms that determine when a motor program is turned on depend on evolutionary conserved structures that regulate both selection and value-based decisions. The detailed circuitry of both the basal ganglia and lateral habenulae and the dopamine innervation had been developed already at the dawn of vertebrate evolution some 560 million years ago, when the lamprey diverged from the line of evolution leading up to mammals and man. Moreover, the projections neurons from the lamprey "cortex" target the same motor areas as in mammals, the basal ganglia, tectum, and the different reticulospinal nuclei and the rostral spinal cord.

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ABSTRACT: LECTURE 1

What Does Our Visual System Know about the World?

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The image formed in our eyes poses a fundamental problem for vision. Different objects can produce very similar images, and the same object can produce drastically different images across viewing conditions. How does our visual system overcome this problem? I will argue that the visual system solves this problem by incorporating systematic knowledge about the external world. I will show two instances of this principle through neuronal recordings in monkey visual cortex: (1) Neurons in the inferior temporal cortex (IT) respond similarly to 3d views of objects, embodying the knowledge that the image of an object changes systematically with rotation in depth; (2) IT neurons encode relative rather than absolute size, embodying the knowledge that the image of an object scales uniformly with depth.

ABSTRACT: LECTURE 2

Developmental Plasticity of Vestibular Circuits Regulates the Behavioral Outcome of Spatial Coding

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The formation and hardwiring of neuronal networks for a specific function are dependent on sequential maturation of excitatory and inhibitory elements in the neural circuit. However, it is unclear if synaptic plasticity of individual elements in a developing sensory circuit is sufficient to impact on behavioral outcome. We hypothesize that synaptic efficacy of vestibular neurons undergoes postnatal tuning to sharpen spatial coding for the presentation of relevant behaviors. Whole-cell patch-clamp data from the vestibular nucleus of neonatal rat indicated unsilencing of developing glutamatergic synapses is key to a tunable excitatory synapse. Specifically, we found postsynaptic insertion of AMPA receptor subunit GluA1 that triggered LTP. Blocking this process delayed developmental emergence of negative geotaxis, a gravity-detection orienting behavior. Within this stage of postnatal plasticity, $GABA_A$R-mediated postsynaptic current in vestibular nuclear neurons was excitatory until the shift to inhibitory in the second postnatal week. Neonatal treatment with $GABA_A$ receptor agonist led to decrease in percentage of neurons expressing inhibitory-LTD, contrasting the increase observable in the second postnatal week. The efficacy of these GABAergic synapses could also be scaled by endocannabinoid retrograde signaling. During postnatal periods of plasticity, chronic treatment with glutamate receptor antagonists or $GABA_A$ receptor agonist not only shifted the time for postnatal emergence of negative geotaxis but also deterred the establishment of internal spatial maps in stations of the mature central vestibular system. When these rats reached maturity, they also exhibited deficits in spatial navigation. Similar manipulation in juvenile animals posed no effect. Altogether, within the postnatal period of plasticity, tuning the balance of excitatory-inhibitory synapses in the sensory component of the vestibular network for spatial coding impacts on behavioral presentation of spatial recognition.

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ABSTRACT: LECTURE 3

Functional Division among Prefrontal Areas of Macaque Monkeys

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The neural circuitries in the prefrontal cortex are thought to be critical for the flexible control of behavior in primates, but the mechanisms remain largely unknown. Because the prefrontal cortex is composed of multiple areas each with unique anatomical connections with other brain sites, we expect that the comparison of functional roles among the prefrontal areas would help disentangle the processes of flexible behavioral control.

Application of previously learned behavioral rules beyond simple stimulus-action is required in goal-directed behavior in complicated environment, and the currently relevant rule is often not directly indicated by sensory cues. The Wisconsin Card Sorting Test (WCST) mimics such a situation. We have developed an animal version of WCST and trained macaque monkeys with the task. In the task, the monkey selected one of the three test stimuli by matching it with the sample stimulus in color or in shape. The matching rule was constant within a block of trials, but changed between blocks without giving any notice to the monkey. There was no cue to indicate the currently relevant rule: the monkey had to determine the rule based on the reward history in recent previous trials. Lesion-behavioral studies and single-cell recordings from intact monkeys have been conducted: these two methods are complimentary with each other. Bilateral lesion of the principal sulcus region (PS), orbitofrontal region (OFC) or anterior cingulate cortex sulcus region (ACCs) resulted in significant degradation of the overall performance of the monkeys. Further analyses of the monkeys' performance in the task and in other probe tests showed that the reasons of the degradation were different among the lesion groups. Only the PS lesion impaired maintenance of abstract rules in working memory; only the OFC lesion impaired rapid learning of rule value from a single success; and the ACS lesion impaired slowing responses under uncertainty. These results show that the prefrontal areas contribute to the flexible control of behavior by playing individually specific functional roles.

We have also expanded our lesion study to the frontal pole (area 10). Based on its anatomical connections, the frontal pole is assumed to be located at the highest level in the cortical hierarchy. Monkeys with the frontal pole lesion didn't show degradation of the WCST performance, whereas they were more efficient in conflict adaptation (faster reaction time, which means a better control after an experience of conflict) and less disturbed by experimentally inserted disturbances (face detection task trials or free rewards given during inter-trial intervals). On the other hand, the frontal-pole-lesioned monkeys were very slow in learning a new rule after extensive learning of a few current rules. These results suggest that the frontal pole works in disengagement of cognitive resource from the current task to new possibilities, whereas posterior prefrontal areas contribute to the execution of the current task.

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ABSTRACT: LECTURE 4

Pathogenesis and Therapy for Alzheimer's Disease (AD) and Parkinson's Disease (PD)

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The Carboxy-terminal fragments of amyloid precursor protein (APP- CTFs), have been found in AD patients' brain and reported to induce apoptosis in neuronal cells. We proposed the hypothesis that CTFs might importantly contribute to pathogenesis of AD by different mechanisms from Aβ.

To investigate the regulatory genes responsible for the neuropathology in AD, we performed microarray analysis with APPV717I-CT100 transgenic mice and isolated the S100A9 gene. We found that the inflammation-related S100A9 gene is significantly upregulated in the brains of AD animal models and human AD patients. In addition, we established a new transgenic animal model of AD by crossbreeding the Tg2576 mouse with the S100A9 knockout (KO) mouse. Our results suggest that S100A9 is responsible for the neurodegeneration and cognitive deficits in Tg2576 mice. The mechanism of S100A9 is able to coincide with the inflammatory process. These findings indicate that knockout of S100A9 is a potential target for the pharmacological therapy of AD.

Recent studies of stem cell show its therapeutic potential for neurodegenerative disorders. Here, we used autologous human adipose-derived stem cells (hASCs) and examined whether intravenously or intracerebrally transplanted hASCs could have therapeutic and preventive effects in Tg2576 mice. We first report that intravenously or intracerebrally transplanted hASCs significantly rescues memory deficit and neuropathology in the brains of Tg mice. More importantly, our findings that transplanted hASCs prevent or delay the onset and progression of the disease strongly suggest that the simple, convenient and safe intravenous injection of hASCs can be very useful in both the prevention and treatment of AD.

In this study, while the memory impairment and pathological features in 15-month-old Tg2576 mice, AD animal mice were not improved by the transplantation of neural stem cells (NSCs). However, NSC-transplantation into 12-month-old Tg2576 was able to prevent learning and memory deficits and Aβ neuropathology by reducing the levels of Aβ, APP-CT, and phosphorylated tau, while increasing anti-inflammatory IL-10, endogenous neurogenesis, and synaptic and dendritic stability.

Overall, these results strongly suggest that the prevention of the disease's progress at the early stages is important for stem cell therapy in AD.

PD is caused by the progressive degeneration of dopaminergic neurons and is characterized by cytoplasmic inclusions known as lewy bodies in the substantia nigra. In many studies, it has been described that the structural and functional alteration of mitochondria were associated with neurodegenerative diseases including PD. Therefore, we investigated the effects of intra-venous injection of hASCs on mitochondrial functions in PD mouse model. Intravenous injection of hASCs greatly improved behavior and mitochondrial dysfunction in PD mice model.

Keywords: AD, PD, Pathogenesis, Gene and Cell therapy.

ABSTRACT: LECTURE 5

Large-scaled Network Reorganization during Recovery from Partial Spinal Cord Injury

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After brain or spinal cord injuries, patients once experience severe paralysis but significant functional recovery can occur through rehabilitative training, however, the underlying neuronal mechanism is still not well understood. We have been studying the neuronal mechanism of recovery after partial spinal cord injury using non-human primate model combining multidisciplinary approaches.

It is generally accepted that direct connection from the motor cortex to spinal motoneurons is first established in higher primates through evolution and the direct pathway has been supposed to be the basis of dexterous hand movements in these species. However, in addition to the direct pathways, there exists an indirect pathway mediated by propriospinal neurons (Alstermark and Isa, 2012). Recently, we clarified that after lesion of the direct pathway, such indirect pathway can compensate for the dexterous hand movements, first by classical lesion experiments, and more recently by a newly developed genetic tool that enabled pathway-selective and reversible transmission blockade with double viral vectors in macaque monkeys (Kinoshita et al. Nature, 2012). Moreover, we showed that various cortical areas including ipsilateral M1 and ventral premotor cortex are causally involved in the functional recovery (Nishimura et al. Science, 2007). In addition, we found that ventral striatum (VSt) including the nucleus accumbens increases the activation during the recovery in association with the motor cortex (Nishimura et al. PLos One 2011), and causally contributes to the recovery by local inactivation technique. This may underlie the mechanism of how the motivation facilitates the functional recovery. Such knowledge about the systems underlying the recovery will contribute to development of novel therapeutic strategies against the neuronal damage.

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ABSTRACT: LECTURE 6

Ischaemia-Induced Neuronal Cell Death is Mediated by Molecular Targeting of CaMKII Phosphorylated at T253

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Calcium-calmodulin stimulated protein kinase II (CaMKII) is a Ca^{2+} activated multifunctional Serine/Threonine protein kinase that regulates many cellular functions including, in neurons, synaptic plasticity and learning (1-4). Ischaemia/excitotoxicity produces a persistent activation of CaMKII and inhibiting this persistent activity post-injury is strongly neuroprotective *in vitro* and *in vivo* (5,6) showing that CaMKII is a major mediator of ischaemia/excitotoxicity-induced cell death. The aim of our work is to understand the molecular mechanisms involved in the CaMKII-mediated cell death in order to identify new drug targets that may be neuroprotective after ischaemic injury such as stroke.

CaMKII is regulated by multi-site autophosphorylation (at T253, T286 and T305/306) and molecular targeting (binding to particular protein partners)(7,8). Targeting can have two functional effects: (i) localising CaMKII to specific cellular microdomains thereby directing its activity towards specific molecular targets to produce specific cellular outcomes; (ii) altering the activity of CaMKII – either inhibition or activation. Phosphorylation and targeting can modify each other.

As CaMKII phosphorylation at T286 is known to persistently activate CaMKII (7), it has been assumed that the ischaemia-induced persistent CaMKII activity is mediated by T286 phosphorylation. However, our results indicate that phosphorylation of CaMKII at T253, which regulates CaMKII activity by molecular targeting (8,9), is the mechanism involved in mediating ischaemia-induced cell death.

Brain regions with enhanced sensitivity to ischaemic damage show enhanced ischaemia/excitotoxicty-induced phosphorylation of CaMKII at T253 but not T286 or T305/306 (9). Following transient occlusion of the Middle Cerebral Artery (MCAo) in rats, T253 phosphorylation is rapidly enhanced in striatum (a region sensitive to ischaemic damage), but not cortex (a region relatively resistant to ischaemic damage), and remains elevated throughout the ischaemic period and for several hours afterwards. By contrast, ischaemia induced elevation of T286 and T305/306 phosphorylation is the same in striatum and cortex and not maintained during the ischaemic period (9). Following excitotoxic stimulation *in vitro* of slices of striatum and cortex the regional differences in CaMKII responses are reproduced showing that they are due to intrinsic differences in the tissues, not a difference in blood perfusion (9). Recently, we have also examined MCAo in transgenic mice that lack the ability to phosphorylate CaMKII at T286 and shown that the absence of T286 phosphorylation did not significantly reduce the infarct volume.

ABSTRACT: LECTURE 6

To test whether persistent activation of CaMKII following ischaemia is mediated by T253 phosphorylation and targeting we have established an *in vitro* model using inducible expression of mutant forms of CaMKII expressed by differentiated neuroblastoma (SHSY5Y) cells that resemble dopaminergic neurons. Differentiated SHSY5Y cells show dose and time dependent glutamate-induced excitotoxic cell death. Induced expression of T253D αCaMKII (mimics T253 phosphorylation) significantly enhanced the glutamate induced cell death. By contrast, induced expression of T253V αCaMKII (prevents T253 phosphorylation) prevented the enhanced cell death and induced expression of T286D αCaMKII (mimics T286 phosphorylation) had no significant effect on glutamate induced cell death.

These results support the conclusion that ischaemia induced phosphorylation of CaMKII at T253 produces a persistent activation of CaMKII by molecular targeting and suggests that the interaction between pT253-CaMKII and its binding proteins may provide a therapeutic drug target in stroke.

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ABSTRACT: LECTURE 7

The Role of Orexinergic Projections to the Locus Coeruleus Nucleus in Morphine Tolerance and Dependence

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Orexin is involved in morphine-induced physical dependence and withdrawal. The locus coeruleus (LC) nucleus receives dense orexinergic projections, and is shown to express orexin receptors type-1. LC is also a key brain region implicated in morphine tolerance and dependence. However the role of orexinergic transmission at the LC nucleus in morphine dependence and tolerance is unknown.

We are studying the effect of orexin neuropeptide at the locus coeruleus nucleus in naloxone-induced morphine withdrawal syndrome and tolerance to the analgesic effect of morphine, using behavioral, extracellular and whole-cell patch clamp recording techniques in rats.

The tail flick test using thermal nociceptive stimulation of the tail showed that central administration of orexin receptor type-1 antagonist SB-334867 inhibits the development of tolerance to antinociceptive effect of morphine. Using in vivo extracellular single unit recording, we found that i.c.v. injection of SB-334867 prevents the development of tolerance to morphine in locus coeruleus (LC) neurons. Moreover, our results indicated that intra LC microinjection of SB-334867 prior to each morphine injection or prior to naloxone administration reduces the severity of naloxone-induced morphine withdrawal symptoms.

We also used whole-cell patch clamp recording in rat horizontal slices containing the locus coeruleus nucleus to examine the effect of orexin on synaptic transmission. The results showed that in vitro application of orexin-A increases LC spontaneous firing rate and paired-pulse ratio (PPR). It also decreases spontaneous excitatory postsynaptic currents (sEPSCs) frequency of LC neurons, but did not change sEPSCs amplitude. Our electrophysiological data indicate that orexin-A application decreased evoked excitatory postsynaptic currents (eEPSCs) and evoked inhibitory postsynaptic currents (eIPSCs) in LC neurons synapses.

It is concluded that orexinergic transmission in the locus coeruleus nucleus might involve in the development of tolerance and physical dependence to morphine. Moreover, our results provide in vitro evidences for a critical role of orexin signaling in LC neurons. It can be deduced that these changes in excitatory synaptic transmission may be elicited by presynaptic rather than presynaptic mechanisms.

Keywords: Locus Coeruleus, Orexin, Orexin receptor type-1, Morphine, Tolerance, Dependence, Tail flick test, whole-cell patch clamp recording, extracellular single unit recording.

ABSTRACT: LECTURE 8

Early Adverse Experience and the Development of Psychopathology

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Early adverse experience is associated with an increased life-time risk for the development of psychopathology. Studies with models of early adverse experience such as maternal separation, elevation of postnatal serotonin levels and maternal influenza exposure are associated with increased anxiety and depressive behavior that often persists across the life-span. I will discuss work from our group that highlights a common role for disrupted cortical 5-HT2A receptor function in diverse early adverse experience models. Strikingly, blockade of the 5-HT2A receptor during the adverse experience is sufficient to prevent the emergence of anxiety and depressive behaviors. Exposure to early stress has predominantly been considered deterministic for adverse consequences on emotionality and neuroendocrine stress-responses. However, an alternate school of thought suggests that early stress experience may also evoke adaptive changes that fine-tune neurocircuitry thus facilitating fitness in potentially hostile environments. I will also describe our work that has addressed the emergence of unique, age-dependent changes at the molecular, epigenetic, neurogenic and behavioral level following early stress. These findings underscore the importance of examining the consequences of early stress experience across a life-span, as the ensuing outcomes may vary substantially depending on the temporal window examined. Our findings also raise the intriguing possibility that the trade-off for short-term adaptive effects may be the premature onset of an age-dependent compromise of hippocampal plasticity and cognitive function.

COLLOQUIM

Molecular-motor transport in cells: what is the importance of motor number, and how might this be regulated?

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Much of biological motion can be attributed to proteins called Molecular Motors. These "Motors" are mechano-chemical enzymes that can generate tiny picoNewton forces, and contribute critically to creating and maintaining cellular order and organization. In cells, they typically function in groups. This talk will discuss our experimental evidence for how many motors typically function together in cells, and will then address how group motor function differs from single-motor function, where such differences are likely important, and how the function of the motors can be regulated.