LECTURES

L-1

Channelopathies Related to Epileptic Disorders

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Ion channels are membrane proteins that permit the passive flow of ions down their electrochemical gradient. Within the human genome, these channels are though to be encoded by over 340 human genes. Ion channels expressed in neurons are crucial for regulating several physiological processes including neuronal excitability, regulation of cell volume, neurotransmitter release, sensory transduction, learning and memory. Therefore, ion channel dysfunction can cause diseases in many tissues. Diseases caused by inherited mutations of ion channels localized on neurons are called "neuronal channelopathies". These are particular important since both ligand- or voltage-gated ion channels are attractive targets for many drugs used for the treatment of neurological and psychiatric disorders. This lecture will be focused on channelopathies related to epileptic disorders. Epileptic seizures are induced by abnormal focal or generalized synchronized discharges within the central nervous system. These may result from the imbalance between excitatory and inhibitory circuits. Among the channelopathies involved in epilepsy particular attention will be paid to those caused by single mutations of the beta subunit of voltage dependent sodium channels, responsible for generalized epilepsy with febrile convulsions (GEFS+), of the KCNQ 2 and 3 potassium channels responsible for the benign form of familial neonatal convulsions (BFNC) or the alpha 4 subunit of the neuronal nicotine acetylcholine receptor, responsible for autosomal dominant nocturnal frontal-lobe epilepsy (ADNFLE). Although these familial forms of epilepsies can be distinguished from idiopathic ones by dominant inheritance with high penetrance, the similarity between symptoms suggests that, as for familial forms of epilepsy, at least some forms of idiopathic epilepsies could be explained by defects in ion channels. Discovery of new channelopathies shall provide new insights for understanding the genetic background of epilepsy and to develop new therapeutic tools for the treatment of this common neurological disorder.

L-2

The Use of Mouse Molecular Genetics in Studying Behaviors

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A major aim of modern biology is to understand how normal gene activities give rise to the structure, function, and behavior of complex organisms. Such knowledge will eventually help us understand the mechanisms of diseases, which in turn will reveal potential drug targets for controlling those diseases. Current technologies of gene manipulation fortunately allow making a specific change in a given gene *in vivo*. A gene targeting experiment begins with the generation of targeting vector to modify a cloned gene (usually to stop the function of the gene) by using the recombinant DNA technologies. Next, the targeting vector is introduced into mouse embryonic stem cells, which are totipotent and can be used to generate live animals. Mutant mice generated through gene targeting therefore allow in mammals to study the function of a specified gene in the context of a whole organism. These approaches have been successfully applied to studies of diverse questions in biomedical sciences, including cancer, development, immunology, and lately brain functions and dysfunctions. Here, the practical aspects of gene-targeting experiments will be briefly discussed with some examples from my own group. In addition, I will introduce a variety of methods that can be used to analyze behaviors of the mouse.

L-3

Ca^{2+} Channels in Normal and Abnormal Brain Functions

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Low-voltage activated (LVA) T-type Ca^{2+} channels play crucial roles in the control of cellular excitability under diverse physiological and pathological processes. Recently, studies revealed a novel role of T-type Ca^{2+} channel in the pain sensory pathway by showing that this channel facilitates pain signals in peripheral nociceptors and in the spinal cord. T-type channels are also highly expressed in the thalamus through which noxious signals from spinal cords should pass before reaching the cortex. Upon sensory inputs, thalamocortical relay neurons respond in dual firing modes: either in singular action potentials or in a burst of action potentials clustered together as a high frequency discharges. T-type Ca^{2+} channels are known to excite hyperpolarized thalamic neurons to generate bursts of action potentials. There has been much debate on the role of the thalamic burst firing in the sensory processing. Therefore, it is an open question whether thalamic T-type channels would contribute to the nociceptive signal processing as a signal enhancer or a suppressor. Sensations from viscera, like fullness, easily become painful if the stimulus persists. Mice lacking◎◎1G T-type Ca^{+2} channels show behavioural hyperalgesia to visceral pain. Thalamic infusion of a T-type blocker, mibefradil, induced similar hyperalgesia in wildtype mice. In response to visceral pain, thalamocortical relay neurons evoked a surge of singular action potentials, which then slowly decayed as the burst firing activity mediated by T-type Ca^{2+} channels gradually increased. In ◎1G-deficient neurons, the induced single-spike response persisted without burst firing. These results indicate that T-type Ca^{2+} channels underlie an anti-nociceptive mechanism operating in the thalamus and support the idea that thalamic burst firing plays a critical role in sensory-gating in the thalamus.

L-4

T-type Ca^{2+} Channels in Pain Processing

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The three isotypes of T-type Ca^{2+} channels are expressed in neuronal cells that are known to be involved in pain signaling. Evidence indicates that T-type Ca^{2+} channels may be involved in the pain sensory processing. Studies on the mutant mice lacking◎◎1G T-type Ca^{+2} channels have provided insight into the mechanism how the thalamus control the sensory flow of persistent pain to the cortex. In response to persistent pain, thalamocortical (TC) relay neurons produce a surge of singular action potentials, which then slowly decay in a reciprocal manner to a gradual increase of the burst firing activity mediated by T-type Ca^{2+} channels. In ◎1G-deficient neurons, the induced single-spike response persists in the absence of burst firing, which results in hyperalgesia in the mutant mouse. While these results show the importance of burst firings driven by T-type Ca^{2+} channels in the pain sensory gating in the thalamus, not much is known about how T-type channels are positively involved in pain signaling. In an effort to define the possibility that T-type channels are novel targets for developing analgesic drugs, we have analyzed two knockout mice, ◎◎1G and◎◎1H, for their behaviors against a variety of pains. In addition, I will introduce a project in KIST that aims to develop T-type channel blockers as pain-controlling drugs.

L-5

Issues and Challenges in the Development of Herbal Psychotropic Drugs: *Withania somnifera*

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Herbal remedies have become increasingly common form of alternative therapy. They have been adopted worldwide and used for almost all clinical indications with high hopes and expectations that they cure all ailments with least or no side effects. Their popularity is because of ancient wisdom, easy availability and less expensive as compared to modern therapeutics. However, lack of scientific information on efficacy and safety validation has put them on a scanner in the West. There are more than 80,000 medicinal plants known and nearly 120 plant derived chemical compounds have been developed as modern pharmaceuticals. The recent reports of the West indicate that herbal remedies do have potential adverse effects and herb-drug interactions. It is a challenge for traditional system in India to revalidate ancient claims on modern footing and describe evidence based use for herbal remedies. Development of aswagandha (Aswal®) on pharmacological basis for its clinical use has been described as a case study.

L-6

Memory Enhancing and Antiamnesic Agents from Natural Source

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Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disorder associated with memory deterioration. With increase life expectancy AD is going to be a major health threat to the ageing society across the globe. The neuropathological hallmark of AD include the accumulation of extracellular amyloid plaque containing β-amyloid and intracellular neurofibrillary tangles. The use of complementary medicines, such as plant extracts, in dementia therapy have become increasingly common in the management of Alzheimer's. The presentation reviews some of the facts about Alzheimer's disease, different animal models to screen memory enhancing agents and its implications in therapeutics. The roles of various natural products like aswagandha (*Withania somnifera*), quercetin, Brahmi® and BR-16A® in various animal models have been discussed.

L-7

Cyclooxygenase as a Drug Target in Neurological Disorders: Behavioral and Biochemical Studies

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Cyclooxygenase (COX) catalyses the first committed step in the synthesis of prostanoids, a large family of arachidonic acid metabolites comprising prostaglandins, prostacyclin, and thromboxanes, and is a major target of non-steroidal anti-inflammatory drugs (NSAIDs). Two isoforms of COX enzymes have been identified, a constitutively expressed COX-1 and an inducible, highly regulated COX-2. Recently, cyclooxygenase is known to express in different areas of brain and inhibitors of cyclooxygenase, specifically the COX-2 inhibitors have shown promise in attenuating inflammation associated with brain disorders. Although COX-1 is constitutively expressed in different areas of brain, there is always a conceptual neglect of the role of COX-1 inhibitors in various neurodegenerative and neuropsychiatric disorders. This presentation summarizes our current understanding of COX expression in the central nervous system and the effects of various COX inhibitors (both non-selective as well as selective COX-2 inhibitors) in major neurological disorders such as epilepsy, schizophrenia, drug addiction and stress. It is speculated that COX inhibition will be a useful, ameliorative adjunct in the treatment of most of the neuropsychiatric disorders.

L-8

Phototransduction

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The vertebrate retina has two types of photoreceptors, rods and cones. Rods are more sensitive than cones, but are saturated under the daylight illumination. Cones dominate in the fovea, and their density rapidly decreases towards the retinal periphery. Rods are absent in the fovea, but has higher density in the retinal region near and outside fovea. This is the reason why we have higher visual acuity in the center of our visual field in daylight vision. Both rod and cone cells consist of the outer segment, the inner segment and the synaptic terminal. The outer segment contains thousands of membrane folding called "disks". The inner segment contains a nucleus and mitochondria. On the disk membrane several kinds of membrane proteins exit: photosensitive rhodopsin (photopigment), G-protein coupled transducin and transducin-activated cGMP-phosphodiesterase (PDE). Rhodopsin, a protein consisting of 348 amino acids, is bound with 11-*cis* retinal, a Vitamin A derivative. When rhodopsin absorbs photon(s), retinal is stereoisomerized into *trans* configuration, which activates the opsin, a protein component of rhodopsin. This is the start of phototransduction cascade: activated rhodopsin triggers transducin activation, which in turn activates PDE, which decomposes the intracellular cGMP. cGMP, the concentration of which is high in the dark, binds to the cGMP-gated cation channels in the plasma membrane and cation influx depolarize the photoreceptor. Illumination decreases intracellular cGMP concentration, closes the cGMP-gated cation channels and hyperpolarizes the photoreceptor. Cones and rods release L-glutamate tonically from their synaptic terminals during darkness (when photoreceptors are maintained in depolarized state). Both rods and cones show light- and dark-adaptation. The amount of photopigment is one of the factors to control light sensitivity of photoreceptors. Another mechanism of adaptation is the one controlled by calcium. Calcium ions flowing through the cGMP-gated cation channels (in the dark) elongate the life time of light-activated rhodopsin, whereby increases the light-sensitivity (dark adaptation)

L-9

Visual Receptive Field

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The retina converts the image into the neural signal and, in this process, the individual photoreceptors work as pixels. But the conversion of the image is not simply pixel by pixel. An important function of the retina is to enhance the contrast of the image by lateral inhibition. As a result, a neuron in the early visual system (from retinal bipolar cells to lateral geniculate neurons) has a concentric receptive field with a center-surround antagonism. The receptive field center is usually made of neural convergence of preceding neurons and its size roughly matches to the anatomical size of the dendritic field. The size of the receptive field surround far exceeds the area of dendritic expansion. Many vision scientists agree now that horizontal cells (HCs) contribute to the formation of the center-surround receptive field. HCs have a large receptive field due to electrical coupling. They have AMPA receptors, and a tonic glutamate release from photoreceptors keeps HCs depolarized in the dark. During surround illumination HCs are hyperpolarized. We recently found that pH of the invaginating synaptic cleft of the cone terminal is related to the membrane voltage of HCs (Hirasawa & Kaneko, 2003). It is kept acidic in the dark and is alkalinized by surround illumination. The pH change we found in the retinal slices of the newt disappeared when the slice was superfused with a solution with enriched pH buffering capacity. We concluded that the surround illumination enhances the amount of L-glutamate release from the alkalinized cone terminal (the effect opposite to spot illumination), resulting in the formation of the center-surround receptive field of the second- and higher-order neurons in the visual system. By an imaging technique, we measured the pH of the extracellular space of an HC (pH_o) isolated from the carp retina and found that depolarization of HC acidifies the immediate surrounding of the HC. The mechanisms of pH change are still under study.

L-10

Early Stages of Image Processing in the CNS

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The optic nerve projects to the lateral geniculate nucleus (LGN) after passing through the optic chiasm. At the chiasm the optic nerve originating from the nasal half of the retina cross to the contralateral side, while that originating from the temporal half of the retina remain uncrossed. This arrangement is necessary to stack the visual images received by the two eyes in register. A part of the optic nerve projects to the superior colliculus to activate pupil reflex and eye movement, and to the suprachiasmatic nucleus to synchronize the circadian rhythm. At LGN the input from the left and right eyes still remain independent. The receptive field of LGN neurons is spherical and has the antagonistic center-surround structure as the optic nerve. LGN neurons project to the layer IV of the primary visual cortex (V1), area 17, where inputs from the two eyes converge to a single neuron. Neurons in layer IV (stellate cells) project to pyramidal neurons in layer II and III or pyramidal cells in layers V and VI. Neurons in V1 have elongated receptive fields. They no more respond to uniform light stimuli covering the entire receptive field. They respond selectively to a slit of light or a dark bar having a specific orientation. The preferred orientation is specific to each V1 neurons and covers all directions. The central part of the visual field (corresponding to the fovea of the retina) is represented by a wide area of V1, while the peripheral visual field is compressed into narrow area of V1. V1 neurons are classified into "simple" cells and "complex" cells. Simple cells have a receptive field consisting of an elongated excitatory region flanked by elongated inhibitory regions, or vice versa. The receptive field of complex cells cannot be dissected into excitatory and inhibitory regions. Some simple cells and some complex cells have inhibitory regions at both ends of their receptive field axis. These are called "end stops". In summary, V1 neurons extract the light-dark boundary with specific orientation. Cells with end stops contribute to the detection of corners or end of a line. Neurons in V1 are arranged in columnar organization. Columns consist of neurons with identical orientation selectivity (orientation column) or neurons with identical ocular dominance (ocular dominance column; right or left eye supplying dominant

inputs). These columns can be visualized by autoradiography using deoxyglucose, activity-depending imaging technique or by transsynaptic transport of radioactive proteins. In the cerebral hemisphere nearly 20 independent visual areas are shown. Visual signals are further processed in the temporal association cortex and parietal association cortex.

L-11

DNA Diversity, Disease and Diagnosis

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There is a considerable similarity in the human genome between different individuals. There are also small variations in the DNA sequence which have been associated with differences in disease susceptibility and prognosis. The preponderance of a particular variant of a gene in a group of individuals with a disease may provide a clue to predict predisposition to a specific disease. However susceptibility to complex traits such as mental retardation could be related to the cummulative effects of several genes, with one or more variants of small effect size occuring with a specific frequency within the genome, combined with environmental factors. This implies that the genes responsible for disorders such as learning disabilities may represent the quantitative extreme of the same genetic and environmental factors that cause variation throughout the normal distribution. This lecture covers the main areas of variations in the human genome and their association with disease. Specific reference would be made to the penetrance and expressibility of genes in selected disorders including those with a neurological aetiology. The approach to clinical genetic screening and the diagnostic strategies for these diseases are also reviewed.

L-12

Detection and Characterisation of Genetic Material

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The current approach to the understanding and diagnosis of disease involves identification and characterisation of the candidate disease genes. Various molecular diagnostic methods are used to establish the specific disease risk profiles for several genes implicated in many genetic disorders. These procedures apply the information from the human genome sequence to screen and test for gene aberrations. Given that a sizable majority of the sequenced human genes are expressed either exclusively or preferentially in the brain, neuroscience stands to benefit extensively from this transition to a molecular diagnostic discipline. This lecture highlights the application of molecular biology tools in neurogenetics. It provides an outline of the currently applied "single gene" diagnostic strategies for DNA characterisation and extends to include the significance of the application of some high throughput procedures, in measuring the abundance of DNA and RNA, gene expression analysis and functional polymorphism, for genome analysis of complex traits and common disorders.

L-13

Neuroprotective and Proregenerative Strategies for Spinal Repair

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L-14

Neuronal Basis of Visual Object Recognition

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Information about visual stimuli is processed in two distinct visual cortical streams. The dorsal stream deals with object motion and its attributes and is called the "where" pathway while the ventral stream handles object form discrimination and is called the "what" pathway. Ventral stream includes cortical areas such as V1, V2, V4 and the inferior temporal cortex (IT). IT of primates is thought to be the final visual area in the ventral stream of cortical areas responsible for complex shape discrimination such as face detection. In my talk I shall cover issues related to the nature of visual object representation. I shall present data from my lab that shows how IT cells code shape information of visual objects such as faces. I would particularly describe recent evidence from my lab showing a causal relation between the activity of IT face cells and perceptual decision making. In brief, we have shown that microstimulation of face cell clusters in IT results in a significant shift of the monkey psychometric function in a face-nonface discrimination task. The magnitude of the effect depended upon the degree of face selectivity of the stimulation site, the size of the stimulated cluster of face-selective neurons, and the exact timing of microstimulation.

L-15

History of Neuroscience – In a Nutshell

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Human brain is the most fascinating object of attention, not only for scientists throughout ages, but also for curious minds from several other disciplines. History of Neuroscience, like of another discipline is a continuing journey from mythological concepts about brain and basis of its working to the actual realization of cellular and molecular basis of brain function. Throughout this journey, advancements and application of techniques in molecular and cellular biology, electrophysiology and imaging not only greatly accelerated the understanding of the mechanisms involved in neuronal signaling, development, localization of cerebral functions, memory and cognition, and various diverse functions of the brain, but also led to discovery of underlying etio-pathogenesis of neurological disorders and their treatment. The birth of Modern Neuroscience at the turn of 20th century was heralded by pioneering contributions among others, of neuroantomist Cajal, physiologists Sherington, Adrian and Langely, and neurologists, Charcot and Hughlings Jackson. Later on, Eccles, Katz, Cole and Curtis, Hodgkin and Huxley, Sackmann and Neher, particularly made enormous contributions to the understanding of molecular basis of neuronal function and nature of neuronal communication. Neuroscience itself emerged as a separate and distinct discipline in early 1950's with intelligent rearrangements of the isolated disciplines of neuroanatomy, neurophysiology, neurochemistry, psychology and other areas of biology. This lecture will provide general information on the history of Neuroscience, relating major events, contributions of leading neuroscientists and key discoveries for a diverse gathering of biology students.

L-16

Strategies for Controlling Tolerance to Opioid Analgesia

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Pain treatment with centrally acting opiates is limited by tolerance. Tolerance is a decreasing effect of a drug with prolonged administration of that drug or of a related compound acting at the same receptor. Much interest into the mechanisms of morphine tolerance has thus recently been garnered with efforts focused mainly (and perhaps naively) on the neuronal intracellular cascade. The currently accepted theory dictates a complicated series of actions leading to excessive glutamate signaling via the NMDA receptors and accumulation of intracellular calcium causing increased action of a plethora of mediators including nitric oxide and PKC as well as eventual changes in gene expression. The end result of this cascade is decoupling of the μ-receptor from its associated potassium ion channel (via a G protein) and therefore inability of agonist binding to induce hyperpolarization of the cell. Moreover, the morphine tolerance and dependence are thought to be representative models for studying the plasticity, including the remodeling of neuronal networks. Several studies have been focused on study of the mechanisms and finding the ways to attenuate morphine tolerance. A main part of these studies have concentrated on the observation that tolerance development is delayed in subjects who are suffering from chronic pain. This speech will briefly discuss strategies for controlling development of tolerance to opioids and will specially concentrate on our new finding in which dexamethasone has been able to attenuate morphine tolerance and reverse it. We will also discuss mechanistically on the possible importance of the level of G proteins expression and their regulators.

L-17

Ion Channels and Neurotoxins

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Ion channels are highly specific filters, allowing only desired ions such as calcium, sodium and potassium through the cell membrane. They are intimately linked to all neurotransmission and neurotransmitter release processes, but in disease states often adversely contribute to the disease pathology. The diversity of subtypes, especially those that are upregulated in disease states, makes ion channels a rapidly expanding area of research in therapeutics. Most neurotoxins including conotoxins, scorpion venoms and also synthetic toxins such as organophosphates and ion channel blockers can result in death. However, scientists have managed to turn the tables and found cures in some toxins. For example, conotoxins obtained from the venom, can be used as an alternative painkiller − especially for patients suffering from severe pain and are dependant on morphine. Once infused into the spine, they attach to the neurons and are able to block off pain signals. Furthermore, 4-AP which is a chemical that blocks the fast voltage sensitive potassium channel is one of a handful of drugs that block this particular channel, which is responsible to shortening the action potential generated by sodium currents in neurons. 4-AP increases the duration of action potentials in demyelinated axons and also at the presynaptic terminals of axons. Thus, it increases the safety factor of conduction in the spinal cord and increases the amount of neurotransmitter released per action potential. Therefore, it can increase sensory and motor function in patients with multiple sclerosis. In this overview, the neurotoxic potential of organophosphates active at ion channels and also the effect of 4-AP on neuronal cells and its possible therapeutic potential will be highlighted.

L-18

Differential Gene Expression of Neurotrophins, Their Receptors and Pro-protein Convertases in Brain, Spinal Cord and Neurally Differentiated Bone Marrow Stromal Stem Cells

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Neural-like cells derived from bone marrow stromal cells (BMSC) have potential usefulness in repair of the CNS injuries or diseases. The functional recovery mediated by these cells, however, depends on production and secretion of specific growth factors and their designated receptors. In the present study, we have investigated the expression profile of neurotrophins (NGF, BDNF and NT-3), their high-affinity (TrkA, TrkB, TrkC) and common low-affinity (p75NTR) receptors as well as pro-protein convertases (PC) family (furin, PC1/PC3, PC2, PC4, PC5, PACE4, PC7/LPC, PC9, SK1, 7B2), in undifferentiated and neurally differentiated rat BMSCs as well as in normal and damaged tissues of brain and spinal cord. BMSCs were extracted and expanded by means of their adhesiveness to plastic surfaces. Stemness nature of the cells, acquiring neural phenotype and gene expression profile of the cells were examined and confirmed by flow cytometry, RT-PCR and immunocytochemistry. Also, RNA extracted from Brain and spinal cord of rat and gene expression profile of target genes were evaluated by RT-PCR. All NTs, their receptors and PC genes are expressed in normal brain and spinal cord except for PC4, PC5 and PC9. All NTs, except NT-3, are expressed in un-differentiated cells and their expression continues after differentiation. None of NT receptors is expressed in un-differentiated cells, however, TrkA and TrkB expression is turned on upon the induction of differentiation. The NT common receptor, P75, is transiently expressed within a narrow time point after differentiation, co-inciding with the peak of apoptotic cell death of neural-like cells. Among convertases, PC1/PC3 and PC2 (specific to neural and endocrine cells) as well as PC4, PC5, PC9 and 7B2 are absent in un-differentiated BMSCs. During the differentiation, PC1and PC2 is turned on. In contrast, furin, PACE4, PC7/LPC and SK1 are highly expressed both before and after differentiation.

L-19

Neuroinflammation and Epilepsy

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Inflammation of the central nervous system in cases such as head trauma, infection and stroke has been associated with the occurrence of epileptic seizures. Microglia, the principal immune cells in the brain, readily become activated in response to injury and produce a variety of proinflammatory and cytotoxic factors. The bacterial endotoxin lipopolysaccharide (LPS) is a general stimulator of microglia to release the inflammatory factors. Peripheral or central injection of LPS is used as a model to produce neuroinflammation. We studied the effect of neuroinflammation induced by LPS and some inflammatory mediators on both acquisition and induction of seizures using electrical and chemical seizure models. Our results indicate both protective and convulsant action of LPS and the inflammatory factors including interleukin 1-beta, prostaglandins and nitric oxide.

L-20

Androgens, Estrogens and Cognitive Function

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The first reports of hormonal influences on learning and memory are dated to 1926. By the mid-1970s the notion that male have superior spatial abilities to female was entrenched in both human and animal literature. Many studies have evidenced a functional interrelation between the nervous and endocrine in modulation on mnemonic processes. Neurohormones, like androgens and estrogen have been shown to affect many brain functions including cognitive and mnemonic aspects of spatial processing. The high density of the androgen receptors in fundamental centers of learning and memory, such as hippocampus shows that there must be some relationships between the androgens receptors and cognition aspects. Testosterone which is the most important androgen, plays a role in the organization of behavior during development. Also, it has been shown that androgens cause sex related differences in learning and memory especially during neonatal period. Many biological effects of androgens in the brain require the local conversion of these steroids to estrogen. Testosterone must be aromatized into an estrogen to exert these behavioral effects; the systemic injection of aromatase inhibitor blocks the effects of exogenous testosterone on copulatory and cognitive behavior. Aromatase enzyme encoded by CYP19 gene is responsible for the formation of estrone and estradiol from C19 androgens, androstenedione and testosterone. Testosterone can influence on cognitive performance directly by acting on the androgen receptors or after being converted to estradiol in the CNS. But estrogen can not significantly convert to other steroid metabolite.

L-21

Monoclonal Antibodies; Expression and Their Applications

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Antibodies are the magic tools of diagnosis and therapeutic importance. Manipulation of immunoglobulin has been possible following recombination and the use of genetic engineering. These proteins may be produced with various abilities such as bearing multi-binding site, multi-epitop recognition and being fused to proteins or other compounds of interest. Naturally fluorescent emitting protein such as Green Fluorescent Protein (GFP) and toxic proteins such as pertuses toxin are among these proteins that can be fused recombinantly with IGs in order to exert a new function for mature protein. The so called chimeric protein will exhibit binding as well as diagnostic or therapeutic properties. Use of GFP as a reporter protein has revolutionized the field such that at present much of the knowledge of ligand receptor interaction, intracellular events etc., is generated using fusion proteins accommodating GFP as an important part of the functional protein. Our research group has been active in the field and recombinant immunoglobulin fusion protein since a decade. I will present some of our findings during the period and discus the application of the technology in various area of biological sciences .We have also been able to produce single domain antibody (the so called VHH or nanobodies) from camel immunoglobulin which exhibits interesting properties. I will also present with a brief account of this amazing molecule and its possible application in therapy.

L-22

Stem Cells Therapy in Nervous System Disorders

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Cell therapy is considered as a new strategy for treatment of peripheral and central nervous system disorders which is at infancy and requires more investigation to illustrate the benefits of this technique. These disorders include neurodegenerative diseases such as Parkinson's disease, traumatic injury in the nervous system such as spinal cord injury and sciatic nerve trauma, and other disorders such as epilepsy. Stem cells were used for this purpose including embryonic stem cells (ESCs) and adult stem cells (ASCs). In this presentation, we report the investigations that were done in our laboratory at the Department of Anatomical Sciences at Tarbiat Modares University Tehran, Iran. ESCs were transfected with BDNF and used to treat Parkinsonian rats and the results showed that these cells resulted in decrease in the rotations of Parkinsonian rats. Also, bone marrow stromal cells (BMSCs) were used to treat Parkinsonian rats and the results showed an improvement in the behavioral tests of the treated animals. BMSCs were induced into neuronal phenotype and the results showed an improvement as well. BMSCs were used to treat transected spinal cord injury and the results showed an improvement in BBB behavioral test. A similar results was noticed with contusive spinal cord injury where the cells were delivered intravenously, BMSCs were localized at the traumatic cysts and differentiated into mature neurons, astrocytes and oligonedrocytes. Currently, a trial for the use of BMSCs to treat epilepsy in rat in underway. In addition, BMSCs are also induced into Schwann cells to treat sciatic nerve trauma.

L-23

Experience Dependency of Neural Plasticity

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The nervous system is able to remodel its connections in order to adjust the organism's response to lasting changes in experience. This process is known as experience-dependent plasticity. This plasticity appears primarily during early development when neuronal circuits are originally being made. Development of cortical sensory systems is influenced by environmental experience during a critical period before onset of behavioural function. During this period, neural circuits across several systems display remarkable plasticity to environmental stimulations. Early in development, the basic connections that define these circuits are determined genetically and the developing brain relies primarily on spontaneous activity. With the maturation of the sense organs, the developing brain relies less on spontaneous activity and more on sensory experience. The sequential combination of spontaneously generated and experience-dependent neural activity endows the brain with an ongoing ability to accommodate to dynamically changing inputs during development and throughout life. Other parts of the brain are also influenced by the sensory inputs. An example is the hippocampus, a well-known area of the brain involved in learning and memory. This area receives sensory inputs indirectly, converged on the entorhinal cortex, as well as directly from the neocortex and undergoes a period of postnatal development. Experimental manipulations of sensory experience can have significant effects on the functioning of the resulting circuits and the visual system has been considered as an appropriate system for assessment of the involvement of sensory experience in development of neural circuits.

L-24

New Insights into Reflex Epilepsy

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It has long been recognized that in certain individuals, epileptic seizures can be precipitated by a wide variety of external stimuli. Visual stimuli are by far the most common trigger of these reflex epilepsies. Reflex seizures are provoked by specific sensory stimulus such as sound and light. The modern environment is a rich source of potentially seizure-triggering stimuli, to which people are increasingly exposed at all age worldwide. Typical environmental stimuli include televisions, computers and video games. Since 1985, there have been increasing reports of patients who have had convulsions precipitated by video material in photosensitive epilepsy subjects and in non-photosensitive epilepsy subjects. It is possible that certain non-visual factors associated with video-game play (e.g., emotional excitement, cognitive engagement, stress, prolonged play, associated sleep deprivation and may be fair) have been linked to seizures. These factors have not only been implicated as contributing to the genesis of video-game seizures in individuals who demonstrate visual sensitivity but also as potential independent risk factors in those who do not. Kindling is an animal model of epilepsy induced by repeated stimulation of the brain. The amygdala has been the focus on interest, due in large part to its role in epilepsy induction and in fear conditioning in both human and rats. The purpose of the present lecture is to review Reflex epilepsy and whether low electrical stimulation of footpad of rats or photic stimulation during fear can facilitate kindling susceptibility.

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Learning, Memory and Morphine Addiction

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