CONTRIBUTION OF INDIAN NEUROSCIENTISTS IN USA

Ghanshyam N. Pandey

Introduction

To celebrate the Silver Jubilee of the Indian Academy of Neurosciences the Executive Committee decided that, in addition to various scientific activities, seminars, symposium etc, a scientific issue of the Journal of Neuroscience needs to be published to cover the progress and status of neuroscience research in India. In this context it was also suggested that a chapter dedicated to the contributions of Indian neuroscientists in the United States needs to be included. This was suggested primarily because of the following reasons and rationale: 1) there are a large number of Indian neuroscientists in the United States and a significant portion of these Indian neuroscientists actively participate in the annual meetings of the Indian Academy of Neurosciences as life members and take part in its activities; 2) there is an Association of Indian Neuroscientists in the United States which meets regularly each year during the annual meeting of the Society for Neuroscience and keeps liaison with the Indian Academy of Neurosciences. There is a good collaboration and interaction between this group and the neuroscientists in India and, in fact, in May of 2007, this Association celebrated the Silver Jubilee of the Indian Academy of Neurosciences by holding a one-day national symposium on current perspectives of neuroscience research.

Neuroscience is one of the fastest growing disciplines in biology and behavioral sciences. It is interdisciplinary in nature and includes such disciplines as psychiatry, neurology, psychology, behavioral sciences, molecular and cellular biology as well as biochemistry, pharmacology and physiology. The membership of the Society for Neuroscience in the United States has grown from 1,000 in the early 1970's to almost 30,000 as of the 2007 annual meeting, and it is probably the fastest growing area in any discipline of scientific research.

The development of Neuroscience as a major discipline started in 1950's with development of suitable technologies for studying the working of CNS as well as the discovery of novel psychotherapeutic agents. The interaction of Indian scientists also gradually shifted from England to USA in the post-independence era. Most of the Indian scientists going to USA during that period worked there for a few years before returning to India. Some of them, however, made significant contributions to Neuroscience research even in that short period. For example, KP Bhargava demonstrated the effect of Rauwolfia alkaloids on central vasomotor loci (Bhargava and Borison, 1955). Upon returning to India, he set up an active center of Neuropharmacology at K.G. Medical College, Lucknow. Similarly M.S. Grewal of Amritsar Medical College compared several available procedures for assay of anti-epileptic activity and showed the supra-maximal electroshock seizure test to be the most satisfactory (Goodman et al., 1953a; Grewal et al., 1954). He

was also involved in pre-clinical evaluation of a new anticonvulsant drug primidone (Goodman et al., 1953b) which was subsequently marketed by ICA as Mysoline. Several other Indian Neuroscientists also visited USA for short term training with funding from Foundations like Ford, Rockefeller, Watumull etc.

The second phase of Indo-US neuroscientists interaction, during 1960's saw several Indian scientists deciding to settle down and work in the USA. These included Dr. **S.N. Pradhan** and Dr. **Harbans Lal** both retired and both primarily behavioral neuroscientists examining the effects of drugs of abuse and alcohol. Dr. Pradhan studied the behavioral and EEG effects of ethanol in rats (Ghosh et al., 1987; Ghosh et al., 1989; Ghosh et al., 1990; Ghosh et al., 1991a; Ghosh et al., 1991b). He also examined effects of morphine self-stimulation in rats modified by agents like chloramphenicol (Copeland and Pradhan, 1988; Copeland et al., 1989) . Dr. Harbans Lal primarily conducted research in the areas of behavioral medicine, substance abuse and prolongation of a healthy life span. His research included studies like the effects of $GABA_A$ compounds on mcPP drug discrimination in rats (Gatch et al., 2002) and the discrimination stimulus effects on pentylene-tetrazol as a model of anxiety (Gatch et al 2002).

The current phase of many more Indian neuroscientists settling to work in USA but still maintaining contacts with Indian Institutions started in mid 1970's. The interaction was significantly catalyzed further by the formation of Indian Academy of Neuroscience (IAN). Many Indian neuroscientists working in USA became life members of the Academy and also held positions in the Executive Committee. They regularly attended annual meetings of IANS and symposia organized by them now form an important part of the scientific program of the annual meeting of IANS. Some of the US members have since been elected Fellows of IANS.

The contributions of the Indian neuroscientists to Basic Neuroscience research in USA have not been consolidated so far. Only Patil (2000) reviewed their contributions to Neuropharmacology for a status report sponsored by Indian National Science Academy, New Delhi. Surprisingly no Indian neuroscientist has been included even in a book by S.N. Pradhan (1996) covering contributions by Indians in the USA.

The present review forms part of a status report of Indian neuroscience during the last 2 decades being published by IAN as a part of its Silver Anniversary celebrations, as stated before. Constraint of time and space did not permit the total clinical and basic work of Indian Scientists in the USA to be included in this review. The review has largely limited itself to contributions by basic neuroscientists, particularly of scientists having significant interaction with Indian institutions.

The contributions of the late **M.K. Ticku** and **Joe Marwah** have been summarized first as a tribute to both of them. This has been followed by a summary of the work done by **H.N. Bhargava** and **Rao S. Rapaka** since they are no longer

involved in active research. The contributions of other scientists have been arranged in alphabetical order.

The next issue is how one can include the contributions of such a large number of Indian neuroscientists in the United States. It was a difficult decision, but two guidelines were primarily used: 1) a similar chapter on the contribution of Indian scientists in pharmacology was published in 1992, and it was therefore decided that the contributions of neuroscientists who contributed after 1992 should be discussed; 2) it was also decided that the description of the contribution of those neuroscientists who either responded to the letter of the committee or who are actively connected with the Indian neuroscience will be included. For all other neuroscientists, either more or less renowned, it was decided that it was very possible their name should be mentioned in the Introduction section.

Dr. **Maharaj K. Ticku** made significant contribution in the mechanism of action of ethanol and its dependence in mammalian brain. A bright research career ended with his untimely death in 2007. Dr. Ticku participated in many IAN meetings. Dr. Ticku's major research contributions were to understand and define the molecular mechanisms by which drugs modulate inhibitory and excitatory neurotransmitter systems in the mammalian central nervous system. $GABA_A$ and NMDA receptors belong to a ligand-gated super gene family. He examined the effect of chronic administration of benzodiazepines, barbiturates, neurosteroids or alcohol on regulation of $GABA_A$ receptor binding, function, gene and polypeptide expression (Marutha 2004 and 2005; Mehta and Ticku 2005; Marutha Ravindran and Ticku 2006; Sheela Rani and Ticku 2006; Qiang et al 2007; Wang et al 2007). Chronic drug treatment could affect neurotransmission by down- or upregulation of receptors, altered coupling between various sites associated with oligomeric receptor complex and/or altered receptor efficacy. How alcohol regulates NMDA gene expression is a major focus. He also established how chronic alcohol alters gene expression of NMDA receptors at the level of epigenetics, transcriptional factors, subsynaptic distribution and trafficking regulating proteins (Gutala et al., 2004; Marutha Ravindran and Ticku, 2004; Marutha Ravindran and Ticku, 2005; Qiang and Ticku, 2005). These experiments were conducted in mammalian cortical neurons under precisely controlled conditions and independent of pharmacokinetic variability. He also studied the effects of alcohol on NMDA receptor function and gene expression. NMDA receptors are involved in a variety of physiological processes, including maintenance of excitability, neuronal development, learning and memory as well as in the pharmacological effects of alcohol. Different experimental approaches were employed in these studies including receptor binding, 36C1-flux, changes in intracellular Ca^{2+} levels, mRNA and polypeptide level measurements. Current research involves regulation of promoter activity of NMDA R2B gene by enhancers and silencing factors (Qiang et al 2005; Rani et al 2005).

Dr. **Hemendra N. Bhargava** is a distinguished neuroscientist who retired from the College of Pharmacy, University of Illinois at Chicago in the early 1990s.

His research was mostly devoted toward an understanding of the mechanism of opiate addiction. He carried out a series of neurochemical and behavioral studies, primarily in rodent models, elucidating the mechanism of opiate dependence related to such important measures as nitrous oxide synthase (NOS), dopamine transporters, noradrenergic receptors and cyclic GMP.

He showed that morphine induced an acute change in the NOS activity in the brain region and spinal cord which is related to enhanced motor activity (Kumar and Bhargava, 1997). He also showed that chronic administration of morphine and enkephalin produced increases in cyclic GMP level in brain regions whereas enkephalin produced decreases in brain regions and spinal cord. These results implicated that alterations of cyclic GMP levels by ì, ê and ä opioid receptor agonists are consistent with the behavioral results with NOS inhibitors on tolerance to ì, ê and ä opiod receptor agonist. Dopamine has been implicated in opioid dependence and Bhargava et al (1996) showed chronic administration of morphine causes changes in the dopamine transporter function in selected brain regions and that these changes are dependent upon whether or not the animals are undergoing the abstinence syndrome.

Dr. **Joe Marwah**, who recently passed away, was an administrator with The National Institute of Health (NIH) during the latter years of his career. He was involved in the evaluation and funding of neuroscience research by NIH as he was the branch chief of the Brain Disorders and Clinical Neuroscience Division of the Center for Scientific Review. However, before taking up the position at NIH he was an active researcher, a distinguished neurophysiologist who carried on research on the understanding of the neurophysiological studies of drugs of abuse, especially cocaine and opioids. He studied the effect of chronic administration on noradrenergic locus coeruleus (LC) neurons in the cocaine-treated and sham rats and found that cocaine treatment attenuates the two alpha 2-adrenoreceptors-mediated responses, most likely via an interaction with central catecholaminergic neurotransmission. He also studied the pre- and post-synaptic actions of cocaine on a central noradrenergic synapse (Pitts and Marwah, 1987). Another of his studies included the autonomic actions of cocaine (Pitts and Marwah, 1989).

Dr. **Rao S. Rapaka** is a science administrator with the National Institute of Drug Abuse (NIDA) and has stimulated neuroscience research in the area of drug abuse for many years. In addition, he has also conducted some research on central actions of drugs of abuse, besides developing many bioanalytical techniques related to drug abuse research. Most recently, he has been working on targeted lipidomics in the CNS (Rapaka et al., 2005). He has also worked on the molecular basis of cannabinoid activity (Makriyannis and Rapaka, 1990).

Dr. **Subimal Datta** at the Boston University School of Medicine in Boston is engaged in research aimed at understanding of neurobiological mechanisms that regulate rapid eye movements (REM) sleep as well as how information is

processed and stored as long-term memories. His initial work was related to the brain stem cholinergic cells and their involvement in REM sleep generation and cortical activation. His team provided the first direct evidence for understanding how the physiological activity of cells within the cholinergic cell compartment of the pedunculopontine tegmentum (PPT) and lateraodorsal tegmentum are regulated for the generation and maintenance of REM sleep (Pare et al 1990; Steriade et al 1990a; Steriade et al 1990b; Datta et al 1991b; Datta 1995). He also discovered two other important aspects of basic neuroscience by identifying the cellular location of the ponto-geniculo-occipital (PGO/P-wave) wave generator in the brainstem by determining the exact cellular location and mechanisms for the generation of PGO-wave (Datta et al 1992; Datta and Hobson 1994; Datta and Hobson 1995; Datta 1997; Datta et al 1998, Datta et al 1999). While identifying the PGO wave generator he also discovered an important part of the brainstem where M2 receptor mediated activation induced a change in REM sleep that lasted for 7 to 10 days (Datta et al 1991a; Calvo et al 1992; Datta et al 1993; Quattrochi et al 1998). This long lasting REM sleep regulating mechanism has an important implication in neuronal plasticity research and for a number of drugs that treat psychiatric and neurological disorders. He has further continued his studies on the understanding of the mechanistic view of the molecular of mechanisms of REM sleep generation (Datta 2002; Datta et al 2003; Datta et al 1997; Datta et al 2001; Datta and Prutzman 2005; Datta and Siwek 1997; Datta and Siwek 2002; Datta et al 2002). They also found an important on-switch in the brainstem that is critical for the activation of hippocampus and amygdala to reprocess memories to be stored in the long-term memory (Datta 2000; Datta et al 2004; Datta et al 2005; Saha and Datta 2005; Ulloor and Datta 2005). He has continued to unravel the cellular, network and molecular mechanisms that are involved in interaction between brainstem switch and parts of the forebrain areas, like dorsal hippocampus, amygdala and medial prefrontal cortex (Datta, 2000; Datta et al., 2004; Datta et al., 2005; Saha and Datta, 2005; Ulloor and Datta, 2005).

Dr. **Jitendra R. Dave** from the Division of Psychiatry and Neuroscience at the Walter Reed Army Institute of Research in Silver Spring, MD, characterized and defined histopathological changes caused by experimental penetrating ballistic-like brain injury (PBBI, A militarily relevant brain injury model), defining three phases of injury during the first 7 days post-injury (Williams et al., 2005). He also defined the time course of caspase-3 activity following a PBBI and related apoptosis cascade. 2-D gel electrophoresis maps have identified 490 proteins from brain tissue samples with altered levels at 24h following PBBI (Liu et al., 2006). MALDI-TOF-MS analysis has identified several of these proteins and the majority of these are associated with various kinases, apoptosis, inflammation, neuronal synaptic plasticity, signal transduction, transcription factors, endopeptidase inhibitor activity, ion transport, and lipoprotein metabolism. Other identified proteins were associated with general cytosolic function. Preliminary results using PowerBlot (a protein array technique) analysis indicate that out of 980 screened proteins, expression

changes occurred in 20 proteins following PBBI and in 22 proteins following ischemic (MCAo) injury (Yao et al 2005; Liu et al 2006; Williams et al 2006a; Williams et al 2006b;). In each case about half of the affected proteins were up-regulated and half down-regulated. However, 12 of the altered proteins were distinct between injury models. One important finding of this study was the discovery that precursor protein of EMAP II (endothelial monocyte activating protein) levels in brain and serum are significantly increased (1.7-1.8 folds) following PBBI, but decreased (2.1-2.3 folds) after ischemic (MCAo) injury compared to the relative shams. Using signal pathway specific DNA microarray, demonstrated differential expression of inflammatory (18 up and 8 down) and apoptotic (9 up and 4 down) genes in the injured brain hemisphere (±2 fold change from sham controls) following PBBI. Similar to microarray results, QRT-PCR data indicated an early increase in expression of the cytokines IL-6, TNF-á, and IL-1â; the cellular adhesion molecules E-selectin and ICAM.

Dr. Dave discovered and characterized effects of NNZ-2566 (an analogue of glypromate, Neuren Pharmaceuticals) to improve neuro-function and protect against secondary neuropathology caused by experimental PBBI (Chen et al 2005). He also completed the 12h infusion dose-response study of NNZ-2566 in the PBBI model of brain injury and nearly completed the therapeutic time window study of NNZ-2566 in the PBBI model. Dr. Dave initiated mechanistic studies with NNZ-2566 (effect of NNZ-2566 on caspase-3 activity, inflammatory cytokines) demonstrating that NNZ-2566 significantly decreased PBBI-mediated increase in caspase-3 activity in a time related manner.

In a recent study, Dr. Dave investigated the effects of PAN-811 (Panacea Pharmaceuticals, Gaithersburg, MD), in four different in vitro models of neurotoxicity (Chen et al 2005). Primary cortical neurons were isolated from 17-day old SD rat embryos and maintained in a serum-containing (BME/HAMS F-12K) medium. Neurotoxicity was induced using hypoxia/hypoglycemia (H/H), veratridine (10 ìM), staurosporine (1 ìM) or glutamate (100 ìM), which resulted in 72%, 67%, 75% and 66% neuronal injury, respectively. Pre-treatment of neurons with PAN-811 (1-100 ìM) for 24hr provided significant dose-dependent neuroprotection against all four of the insults. A maximal neuroprotection of 89%, 42%, 47% and 89% was observed at 10 ìM PAN-811 concentration against H/H, veratridine, staurosporine and glutamate toxicities, respectively. Cytochrome c is released from the mitochondria into the cytosol as a result of cell exposure to glutamate or H/H. This release was blocked by pretreatment of neuronal cells with PAN-811. Furthermore, pretreatment of cultured cortical neurons with 10 µM PAN-811 produced a time-dependent increase in the protein level of the anti-apoptotic gene bcl-2. This up-regulation of bcl-2 following PAN-811 treatment was evident even after glutamate or H/H treatments. An up-regulation in the expression of the pro-apoptotic p53 and bax genes was also observed following these neurotoxic insults, however, this increase was not suppressed by PAN-811 pretreatment. The functional inhibition of bcl-2 or Bcl-2 by HA14-1 reduced the neuroprotective efficacy of PAN-811. Finally, PAN-811 treatment

also abolished glutamate or H/H-mediated internucleosomal DNA fragmentation. These findings strongly suggest that suppression of cytochrome c release and bcl-2 up-regulation are prominent factors in PAN-811 neuroprotection against glutamate or H/H toxicities.

The major research focus of Dr. **Yogesh Dwivedi,** Associate Professor of Psychiatry and Pharmacology, Department of Psychiatry, University of Illinois at Chicago, is to examine and identify the molecular and cellular nature of events in the brain that may lead to suicidal and depressive behavior. His research is based upon the hypothesis that abnormalities in cellular signaling may serve as critical vulnerability factors that may predispose a person to suicidal and depressive behavior (Dwivedi, 2006). More specifically, he hypothesizes that abnormalities in cell survival pathways may lead to abnormalities in synaptic plasticity and brain structure, and thus to depressive and suicidal behavior (Dwivedi, 2006; Dwivedi, 2008). He has further hypothesized that an abnormal functioning of hypothalamic-pituitary-adrenal (HPA) axis and stress may regulate the signal transduction molecules that play an important role in causing such abnormalities. Utilizing various investigative approaches, namely, human postmortem brain; peripheral blood cells, and pre-clinical animal models, Dr. Dwivedi has successfully integrated basic and clinical neuroscience.

He is the first to demonstrate reduced transcriptional activation and expression of CREB, expression of trophic factors, and activation of cognate Trk receptors in postmortem brain of suicide subjects (Dwivedi et al., 2003a; Dwivedi et al., 2003b; Dwivedi et al., 2005b; Dwivedi, 2008;). His findings that cell survival pathways mediated by extracellular signal-regulated kinases (Dwivedi et al., 2001; Dwivedi et al., 2006a; Dwivedi et al., 2006b; Dwivedi et al., 2007) and PI 3-kinase and that various apoptotic regulatory proteins are abnormally expressed in postmortem brain of suicide subjects (Dwivedi et al., 2008) supports the hypothesis that suicide brain is associated with cell death, which may consequently lead to altered synaptic and structural plasticity of brain. In addition, he has reported many seminal findings that clarify the roles of serotonergic receptors and of signaling systems, such as phosphoinositide (Dwivedi et al., 1998) and adenylyl-cyclase cAMP (Dwivedi et al., 2002a; Dwivedi et al., 2004b), in the pathophysiology of depression. Dr. Dwivedi has done extensive studies as how overactive HPA axis may play a role in depressive behavior. In animal models, he has shown that alterations of the HPA axis or stress-induced behavioral depression in rats brings about changes in several components of signaling systems in brain similar to those observed in suicide brain or in peripheral tissues of suicidal and depressed patients (Chen et al., 2006; Dwivedi et al., 2004a;Dwivedi et al., 2005a; Dwivedi et al., 2005c; Dwivedi and Pandey, 1999a; Dwivedi and Pandey, 1999b; Dwivedi and Pandey, 1999c; Dwivedi and Pandey, 2000), which suggests that manipulation of the HPA axis or stress might be playing a role in modulating signaling mechanisms. His recent studies that psychoactive drugs differentially regulate the expression of specific isozymes of the important phosphorylating enzymes protein kinase C

(Dwivedi and Pandey, 1999b), phospholipase C (Dwivedi et al 2002a), and protein kinase A (Dwivedi et al., 2004a), and that expression of specific subunits of G proteins (Dwivedi et al., 2002b) are altered in rat brain show that mechanism of action of psychoactive drugs lie at the level of signal transduction mechanisms. In addition, Dr. Dwivedi has developed animal models of depression and PTSD, which have provided meaningful insight into the neurobiology of these disorders. More recently, utilizing microRNA and epigenetic approaches, his group is focusing to unravel the molecular mechanisms that may be responsible for gene regulation in depressed and suicide brains.

In summary, by successfully integrating basic and clinical neuroscience research, Dr. Dwivedi has provided new insights into the molecular and cellular mechanisms that may serve as important vulnerability factors in the pathophysiology of depression and suicide.

Dr. **Anumantha Kanthasamy**, from the Iowa State University in Ames, has focused his research work on identifying the cellular and molecular mechanisms underlying dopaminergic degeneration in *in vivo* and *in vitro* models of Parkinson's disease. Specifically, his basic neuroscience research is focused on two major areas: 1) investigation of the mechanism underlying the environmental, chemically-induced neurodegenerative process as it relates to the etiopathogenesis of Parkinson's disease (Choi et al., 2006), and 2) characterization of the role of metals in the pathogenesis of prion diseases (Choi et al., 2006). Dr. Kanthasamy's preclinical neuroscience research focuses on development of novel therapeutic strategies in the treatment of Parkinson's disease and posthypoxic myoclonus. A number of translational approaches, including pharmacological agents, gene therapies, and RNAi mediated knockdown strategies, have been employed in both cell culture and animal models of neurological disorders. The preclinical research has resulted in several publications in high impact journals (Kanthasamy et al., 1999a; Kanthasamy et al., 1999b; Kanthasamy et al., 2000; Madhavan et al., 2003; Yang et al., 2004, Sun et.al., 2006; Kanthasamy et al., 2006).

The research interests of **Ashok Kumar** from the Department of Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, involve delineating the brain mechanisms contributing for altering synaptic transmission and their relationship to learning and memory during aging. Synaptic plasticity is thought to mediate the associative and information storage properties of neurons and form the cellular basis of learning and memory. Intracellular calcium (Ca^{2+}) levels play a pivotal role in regulating synaptic plasticity mechanisms and determining the degree and direction of synaptic strength in response to neuronal activity. Interestingly, synaptic plasticity processes modify over the lifespan and consequently could underlie cognitive impairments associated with advanced age. Dr. Kumar's research, mainly focused on the hippocampus, a brain region responsible for short-term memory and is vulnerable to aging process, characterized several biological markers of brain aging associated with memory impairment and provides

a model linking age-related memory decline with dysregulation of Ca^{2+} homeostasis (Foster et al 2001; Foster and Kumar 2002; Kumar and Foster 2002; Sharrow et al 2002; Foster et al 2003; Kumar and Foster 2004; Kumar and Foster 2005).

Dysregulation of the Ca^{2+} homeostasis during aging contributes to various biological markers of brain aging including the shift in synaptic plasticity, decreased neuronal excitability due to an augmented after hyperpolarization (AHP) and spike frequency accommodation, increased susceptibility to neural toxicity, and altered gene regulation. Synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD) is one of the foremost models for the memory mechanisms. The decrease in synaptic strength during senescence may be due to loss of synaptic contacts, decreased transmitter release, and reduced postsynaptic responsiveness to transmitter. Moreover, aging is associated with a shift in synaptic plasticity favoring decreased synaptic transmission in response to neuronal activity and recently they have shown that release of Ca^{2+} from voltage gated Ca^{2+} channels and intracellular Ca^{2+} stores contributes to increased susceptibility to LTD induction. Cell excitability, the propensity to evoke an action potential in response to depolarizing current is reduced in hippocampus of aged animals. Results have provided enough evidence that the decrease in neuronal excitability in aging hippocampal neurons is due to an increase in the magnitude of the Ca^{2+}-dependent, K^{+}-mediated AHP and larger spike frequency accommodation. Recently, they have shown that blocking Ca^{2+} release either from intracellular Ca^{2+} stores or voltage gated Ca^{2+} channels reduced the enhanced AHP. The larger AHP disrupts the integration of postsynaptic depolarization that underlies much of the impairment in LTP and a reduction in AHP is associated with a lowering of the threshold for LTP induction and an increase in the magnitude of LTP. The augmented AHP may interrupt the transmission of information and contribute to decline in cognitive functions during aging.

Dr. Kumar is also interested in delineating the impact of environmental enrichment and exercise on biological markers of brain aging and its effect on cognitive performance during senescence. Results obtained from a recent study suggest that environmental enrichment reduced the augmented AHP in aged animals. In addition, his research also focused on unraveling the pharmacological and biochemical signaling pathways involved in chemically induced LTD by group I metabotropic glutamate receptor agonist, (RS)-3, 5-dihydroxyphenylglycine (DHPG) and cholinergic receptor agonist, carbachol. The results indicate that the magnitude of DHPG or carbachol-induced LTD is enhanced in senescent animals. Induction of DHPG-LTD in aged animals depends on activation of both the metabotropic glutamate receptor 1 and 5 subtypes and requires Ca^{2+} from L-type Ca^{2+} channels. Finally, they also studied estrogen effects on hippocampal function across the lifespan and their results indicate that estrogen rapidly increases neuronal excitability, decreases AHP, and augments the strength of synaptic transmission. Restoration of estrogen receptor alpha function by gene delivery system in the hippocampus of estrogen receptor alpha knock out mice enhances synaptic

transmission and improves memory performance. Thus, taken together his research interest is to delineate the pharmacological, biochemical, and molecular mechanisms underlying biological markers of brain senescence and contributing to cognitive impairments associated with neurodegenerative diseases and aging.

Dr. **Debomoy Kumar Lahiri**'s research team at the Medical Neurobiology section of the Departments of Psychiatry and Medical and Molecule Genetics, at the Indiana University School of Medicine in Indianapolis has primarily focused on the major areas of molecular neurobiology and genetics related to neurodegenerative disorders. He has primarily worked on the mechanism of aging, origin and biogenesis of Alzheimer's amyloid plaques and the general areas of gene regulation of Alzheimer's disease (AD) (Lahiri 2004a; Lahiri 2004b; Lahiri 2004c; Lahiri 2004d; Lahiri et al 2004a; Lahiri et al 2004b; Lahiri and Greig 2004; Lahiri 2005; Lahiri et al 2005; Lahiri et al 2007; Lahiri 2008). The three major areas of Alzheimer's research involve studies of the regulation of important neuronal genes, such as the apolipoprotein (apo-E), â-amyloid precursor protein (APP) and â-secretase (BACE) to determine their roles in the pathogenesis of AD. They have also investigated the processing of APP, BSCE and important synaptic proteins in relation to AD, and the cholinergic system. They have showed that anti-cholinesterase drugs, such as tacrine and phenserine, regulate levels of APP in neuronal cells and *in vivo*, presumably through the 5'-UTR of APP mRNA. They have also cloned and characterized APP, APOE and â-secretase-1 and -2 (BACE1, BACE2) gene promoters, which have good potential in drug development for Alzheimer's disease.

Professor **Sahebarao P. Mahadik** and his colleagues at the Medical College of Georgia, Augusta, Georgia, USA; and his colleagues at the Interactive Research School for Health Affairs, Bharati Vidyapeeth, Pune, India are examining the hypothesis that the increased oxidative stress and reduced growth factors contribute primarily to the neurodevelopmental pathology and treatment outcome of schizophrenia. These studies are done using medication naïve first-episode psychotic and chronic medicated schizophrenic patients and rats treated with or without most commonly used antipsychotic drugs.

In clinical studies they found that increased oxidative stress causes systemic (both brain and body) cellular injury, and therefore markers of increased oxidative stress, reduced antioxidant enzymes in RBC and increased cellular injury, increased plasma lipid peroxides reflect similar changes in the brain. Studies in medication naïve first-episode psychotic and chronic medicated schizophrenic patients from both USA and India have shown that the altered levels of RBC antioxidant enzymes and increased plasma lipid peroxides and decreased levels of essential polyunsaturated fatty acids (particularly omega-3 fatty acid docosahexaenoic acid, DHA) that further worsened by chronic treatment with antipsychotics (Khan et al 2002; Ranjekar et al 2003; Arvindakshan et al 2003). Oxidative stress can be increased by genetic or by a wide range of epigenetic factors such as nutrition, infections, neurotoxins, alcohol, smoking, and social, economic and emotional

stresses during prenatal and early postnatal life that all are reported to be developmental risk for schizophrenia (Mahadik and Mukherjee, 1996; Mahadik et al., 2001). If this situation is not prevented (neuroprotection) in time, these neuropathologies can progress leading to serious behavioral problems and functional disability. Since the brain development and maintenance (neuroprotection) is regulated by several key growth factors, particularly brain derived neurotrophic factor (BDNF), nerve growth factor (NGF) and vascular endothelial growth factor (VEGF) a role for these neurotrophins is implicated in schizophrenia (Buckley et al., 2007). These studies in medication naïve first episode patients have shown that the levels of all of these neurotrophins were reduced in both plasma and CSF, and antipsychotic (typical > atypical) treatment for short-term improved but chronic treatment declined their levels.

In animal studies, using laboratory rats, they focused on the mechanisms of actions of major antipsychotics on markers of oxidative stress, cell injury and neurotrophic factors in brain were studied in rats in order to explain the mechanisms of actions of antipsychotics on neuropathology and clinical outcome in patients. First generation antipsychotics (FGAs) such as haloperidol and chlorpromazine and second generation antipsychotics (SGAs) such as clozapine and olanzapine differed in their time dependent effects on oxidative stress markers (antioxidant defense enzymes and lipid peroxides) and levels and expression of neurotrophins in brain region specific manner. FGAs but not the SGAs reduced the levels of antioxidant enzymes and increased the lipid peroxides in brain with much shorter duration of treatment, <45 days vs >90 days, respectively (Pillai et al 2006). Similarly, FGAs but not the SGAs reduced the levels and expression of neurotrophic factors in brain with much shorter duration of treatment, <45 days vs >90 days, respectively (Pillai et al., 2006). Furthermore, even SGAs had similar effects on oxidative stress markers and neurotrophic factors as FGAs over 180 days of treatment. They also found that switch from FGA to SFA almost normalized the levels of neurotrophic factors and the oxidative cellular damage. The increase in oxidative stress markers paralleled the decreased levels of neurotrophic factors indicating that such mechanisms may be involved in the beneficial or side-effects of these both FGAs and SGAs (Terry et al., 2007). These studies provide clues for the improved novel treatment strategies for schizophrenia.

Dr. Mahadik's research is also directed toward the development of novel treatment strategies for schizophrenia. Recent reports have clearly indicated that in spite of availability of a large number of antipsychotics around the world for the treatment of schizophrenia the clinical outcome is very little improved and the quality of life is not improved at all. This has already directed the attention to augmenting agents and alternative medications, either alone or in combination for a short duration with conventional antipsychotics. Since the neuropathology of schizophrenia involves the neurodevelopmental abnormalities use of neurotrophic agents such as growth factors, erythropoietin and cystamine that improve the levels of neurotrophic factors is relevant (Buckley et al., 2007). Similarly, since

oxidative cell damage/dysfunction is also a major cause of neuropathology of schizophrenia use of antioxidants (e.g., vitamins E and C, and glutathione) is very relevant (Mahadik et al., 2001; Mahadik et al., 2006). In addition, since the membrane phospholipid omega-3 fatty acids (particularly DHA) are predominantly reduced in schizophrenia supplementation of DHA is also highly relevant (Mahadik and Yao, 2006). It has already been reported that adjunctive use of antioxidants and DHA in patients (Arvindakshan et al., 2003; Mahadik et al., 2001) and neurotrophic agents such as erythropoietin and cystamine in rats (Pillai et al., 2008; Pillai et al., 2006) with antipsychotics synergistically enhance and sustain the improve clinical outcome and reduce the side effects of antipsychotics for extended periods of treatment. These studies provide novel pharmacological targets for early intervention with dietary supplementation and neurotrophic agents for the treatment of schizophrenia and prediction of clinical outcome, relapse or remission.

Dr. **Ghanshyam N. Pandey** has been engaged in neuroscience research for close to four decades. The work in his laboratory was focused on exploring the biochemical abnormalities associated with mood disorders and suicide. During these years he has conducted research both in the clinical as well as preclinical aspects of mood disorders. His preclinical studies involve examining the mechanism of action of psychoactive drugs and lithium as well as the studies of the animal models of depression. The clinical studies include research 1) using the postmortem brain samples obtained from suicide victims with or without depression and matched normal control subjects and 2) using the peripheral cells such as platelets and lymphocytes obtained from adult and pediatric patients with mood disorders and 3) using either the animal models of depression or 4) exploring the mechanism of action of psychoactive drugs.

In preclinical studies Dr. Pandey examined if alterations in adrenergic receptor sensitivity are associated with the mechanism of action of antidepressant drugs and reported that either chronic treatment with antidepressant drugs or electroconvulsive shock treatment causes subsensitivity of â-adrenergic receptors in the rat brain (Hu et al., 1980).

Dr. Pandey found decreased â-adrenergic receptors in the leukocytes of depressed patients (Pandey et al., 1987). The results of this study indicated that decreased â-adrenergic receptor responsiveness in depression is probably due to a decrease in the number of â-adrenergic receptor sites. He also found an increase in the number of $á_2$-adrenergic receptors in platelets of depressed patients (Pandey et al., 1989).

One of the earlier findings from the studies to the mechanism of action of lithium was the discovery that one of the pathways of lithium transport known as lithium sodium counter transport is decreased in the red blood cell of manic patients (Schless et al., 1975; Casper et al., 1976). There is a wide variation in the steady-state in vivo distribution of lithium (Li^+) between red blood cells (RBC) and plasma

in patients treated with lithium carbonate. Patients with bipolar illness have higher Li^+ ratios in vivo than normal controls, and that patients who respond to Li^+ treatment have higher Li^+ ratios than nonresponders. Dr. Pandey has developed a simple in vitro method for predicting in vivo RBC/plasma Li^+ ratio (Pandey et al., 1978). The studies of Li^+ transport in human RBCs have resulted in findings that have important implications for the understanding of the pathophysiology of affective disorders and for the clinical use of Li^+.

In family studies, using monozygotic and dizygotic twins he also showed that there is a significant genetic control on lithium/sodium counter transport and that patients who have this kind of abnormality respond to lithium treatment (Dorus et al., 1974; Dorus et al., 1975).

In the early 90's Dr. Pandey's laboratory demonstrated that one of the serotonin receptor subtypes, known as serotonin $(5HT)_{2A}$ receptor, is increased in the platelets of suicidal patients independent of psychiatric diagnosis and proposed that platelet $5HT_{2A}$ receptors could be a potential biological marker for suicidal behavior (Pandey et al., 1990; Pandey et al., 1995). Extending this work to serotonin receptors in the CNS he examined the postmortem brain tissues obtained from suicide victims and normal control subjects and demonstrated that the protein and gene expression of $5HT_{2A}$ receptors is increased in the postmortem brain of teenage suicide victims compared with normal control subjects (Pandey et al., 2002). An extension of these studies in postmortem brain tissue also showed abnormalities of several signaling systems including the phosphoinositide (PI), adenylyl cyclase (AC) and MAP kinase signaling systems. Some of the important findings included the observation of decreased protein and gene expression of protein kinase C (PKC), phospholipase C (PLC), cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) in the postmortem brain of suicide victims (Pandey et al., 1997; Pandey et al., 1999; Pandey et al., 2004a; Pandey et al., 2005a; Pandey et al., 2007; Pandey et al., 2008d). In short, Dr. Pandey's group has found that $5HT_{2A}$ receptors were increased in suicidal patients and in patients with mood disorders. PKC isozymes and activity were decreased in pediatric patients with bipolar illness and protein and gene expression of BDNF was significantly decreased in the platelets and lymphocytes with mood disorders (Pandey et al., 2008b; Pandey et al., 2008e). The studies on MAP kinase signaling have been described in the section of Dr. Pandey's colleague, Dr. Yogesh Dwivedi. More recently, studies with the Wnt signaling pathway indicate abnormalities or glycogen synthase kinase (GSK-3â) in suicide victims and also indicate its role in neurodevelopment (Pandey et al., 2008a) . Most recent studies by his group focused on the abnormalities of the components of the hypothalamic-pituitary-adrenal (HPA) axis and the cytokines in the postmortem brain of suicide victims with depression and normal control subjects.

One of the unique approaches provided by Dr. Pandey's laboratory is reflected in his studies of the neurobiology of pediatric mood disorders and teenage suicide,

both disorders being poorly understood and not properly studied. Using this population, he has studied the components of neurotransmitter signaling systems, such as PKC and BDNF in teenage suicide brain (Pandey et al., 2004a; Pandey et al., 2008c) and protein and gene expression of PKC and BDNF in platelets of pediatric bipolar patients (Pandey et al., 2008b; Pandey et al., 2008e).

The overall aim of the research program of Dr. **Subhash C. Pandey**, professor and director neuroscience of alcoholism research in the Department of Psychiatry, University of Illinois at Chicago and Jesse Brown VA medical center Chicago, is to elucidate the molecular and/or cellular mechanisms involved in ethanol dependence to provide a basis for designing drugs to treat alcohol addiction. The cAMP responsive element binding (CREB) protein gene transcription factor is a common denominator of the signaling cascade for a number of neurotransmitter receptors, whose function is regulated via phosphorylation by cAMP-dependent protein kinase A (PKA) and Ca^{2+}/calmodulin dependent protein kinase IV (CaM kinase IV) as well as by mitogen activated protein kinases. Phosphorylated CREB regulates the expression of downstream cAMP-inducible genes. Neuropeptide Y (NPY) and its receptor NPY-Y1 as well as brain derived neurotrophic factor (BDNF) and its receptor trk-B are CREB-related genes, and NPY acts as a potent endogenous anxiolytic compound. The research conducted in Dr. Pandey's laboratory has provided evidence that decreased function of CREB and its related genes NPY and BDNF in the circuitry of central nucleus of amygdala (a brain area associated with anxiety, fear, and emotion) is involved in anxiety related to alcohol withdrawal in rats (Roy and Pandey, 2002; Pandey et al., 2003; Zhang and Pandey, 2003 Pandey et al., 2008g). In addition they demonstrated that the anxiolytic effects of alcohol were associated with increased expression of activity-regulated cytoskeleton-associated protein (Arc) and increased dendritic spine density in the amygdaloid structures of rats. On the other hand, anxiety related to withdrawal and/or anxiety in general has also been linked to decreased Arc expression and dendritic spine density in the central amygdala (Pandey et al., 2008g). Dr. Pandey's group for the first time demonstrated the role of amygdaloid chromatin remodeling in the anxiolytic and anxiogenic properties of ethanol exposure and its withdrawal, respectively, in rats (Pandey et al., 2008f).

Predisposition to anxiety and alcohol abuse disorders may also involve abnormalities in the signaling cascade pathways that ultimately lead to abnormal gene transcription patterns in the specific neural circuitry of the brain (Pandey, 2003). Dr. Pandey's group has shown that deletion of the CREB gene can promote alcohol intake and also provoke anxiety-like behaviors in mice. They also demonstrated that deletion of the CREB gene can lead to a reduction in the expression of CREB target genes, such as NPY and BDNF, in several brain regions, including the amygdala and nucleus accumbens of mice (Pandey et al., 2004b). These findings were extended in a series of molecular and pharmacological experiments and they found deficits in CREB, NPY, and BDNF in the circuitry of central amygdala were involved in the genetic predisposition to anxiety and alcohol

drinking behaviors (Pandey et al., 2005b; Pandey et al., 2006). On the other hand, deficits in CREB and NPY in the nucleus accumbens shell (a brain area associated with the reward mechanisms of addiction) were involved in promoting alcohol intake, independent of anxiety-like behaviors, in mice and rats (Misra and Pandey, 2003; Misra and Pandey, 2006). Dr. Pandey's group has also demonstrated that the serotonergic system can regulate the abnormal hypothalamic pituitary adrenal axis in alcoholism (Roy et al., 2002). Studies indicated a high correlation between alcohol consumption and smoking. This group also found that CREB gene transcription factor in the amygdala and nucleus accumbens might play a role in nicotine dependence as well.

Thus, the above research has provided crucial information about the neural molecular mechanisms of ethanol and nicotine dependence and the neurobiological basis of genetic predisposition to anxiety and alcoholism.

The research of Dr. **Harish C. Pant**, NIH, National Institute of Neurological Disorders and Strokes, Bethesda, MD, focuses on the neuronal plasticity and the biology of neurodegeneration by studying the regulation and deregulation of neuronal cytoskeletal protein phosphorylation (Li et al 2000; Tanaka et al 2001). The Biology of Neurodegeneration program evolved from a laboratory studying the basic biology of neuronal cytoskeletal protein phosphorylation during development and normal function in the adult. To understand the molecular basis of neurodegeneration our major focus has been to study the regulation of compartment-specific patterns of cytoskeletal protein phosphorylation in neuronal perikarya and axons. These studies have demonstrated that phosphorylation of the numerous acceptor sites on such proteins as Tau and neurofilaments was tightly regulated topographically and generally confined to the axonal compartment. It was recognized that in neurodegenerative disorders such as Alzheimers disease (AD) and Amyotrophic lateral sclerosis (ALS), the pathology was characterized by an accumulation of aberrantly phosphorylated cytoskeletal proteins in cell bodies, suggesting that topographic regulation had been compromised. This led inevitably into studies of neurodegeneration in cell culture and model mice with emphasis on a specific neuronal protein kinase, e.g. cyclin dependent kinase5 (cdk5), that targets numerous neuronal proteins including cytoskeletal proteins, which when deregulated, may be responsible for the pathology seen in neurodegeneration. In cell systems, neuronal stress leads to deregulated kinases, for example, cdk5, accompanied by abnormal cytoskeletal protein phosphorylation and cell death characteristic of neurodegeneration. Recently they have developed peptides derived from, p35, a neuron specific activator of cdk5, have been developed for deregulated cdk5 activity which rescue cells in vitro from this stress induced pathology. The questions currently being investigated are (1) How is cytoskeletal protein phosphorylation topographically regulated in neurons? (2) What factors are responsible for the deregulation of cdk5 in neurons? (3) Can mouse models of AD and ALS be treated therapeutically with peptides that specifically inhibit deregulated cdk5 and then extended to human subjects?

Dr. **Mohammad I. Sabri** at the Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University has primarily worked in the area of neurotoxicity. Although his earlier work involved basic research on the biology of myelin and its degeneration in multiple sclerosis (MS) and experimental allergic encephalomyopathy (EAE) (Ochs et al 1969) however, his later work focused primarily on the mechanism of action of environmentally significant chemical toxins such as 2,5-hexanedione and acrylamide (Sabri and Spencer 1990). His studies suggested that interruption of axonal transport mechanism jeopardizes neuronal structure and functions and leads to nervous system disorders. More recently, he has focused on the neurotoxicity of non-chlorinated solvent metabolite 1,2-diacetylbenzene (1,2-DAB) where he had delineated the relationship between the chromogenicity and neurotoxicity of aliphatic and aromatic hydrocarbons. They found that the colorless 1,2-DAB forms a blue pigment on contact with proteins and tissues and that fetal exposure resulting intraspinal axonal swellings and this swelling appears to be similar to intraspinal pathology seen in the amyotrophic lateral sclerosis (ALS). They are currently involved in studying the structure-activity relationships for the chromogenic and neurotoxic properties of the aromatic and aliphatic solvent metabolites. More recent studies include genomic studies using gene-chips and proteomic studies to discover gene/ protein signatures associated with toxic neuropathy.

Dr. **Dipak Sarkar** at Rutgers, The State University of New Jersey, has focused on determining the body's mechanisms of coping with stress and how stress alters immune and reproductive functions, and induces drug-seeking behavior and promotes cancer. This work has contributed significantly to the understanding and treatment of various stress-induced diseases. He demonstrated that the luteinizing hormone-releasing hormone (LHRH) is released in the cyclic fashion from the hypothalamus into the blood of pituitary portal vessels and that the same hormone regulates the secretion of pituitary gonadotropin and maintains the reproductive cycle (Sarkar et al., 1976). He has also shown that stress, lactation, and pituitary tumors, that increase blood levels of prolactin, also inhibit LHRH secretion and induce hypogonadism. These studies have helped establish the role of LHRH in reproduction. He and his coworkers also demonstrated that the formation of prolactin-secreting pituitary tumors (prolactinomas) are associated with the loss of functional dopamine neurons in the hypothalamic tissue of aging animals and in animals given high amounts of estrogen (Sarkar et al., 1982). They also show that dopaminergic agents prevent the growth of prolactinomas. These studies have helped elucidate why some people are sensitive to tumor promoting action of estrogen while others are not. Dr. Sarkar's work has helped to understand the cellular and molecular mechanisms involved in the development of estrogen-induced prolactinomas by showing the critical role of peptides related to the transforming growth factor beta (TGF-â) in tumorigenesis (Sarkar et al., 1992) and that TGF-â1 peptide may be useful in the treatment of prolactinomas (Sarkar et al 2005).

Dr. Sarkar's laboratory has also been involved in studies of molecular mechanisms of alcoholism. Some of the important studies include a finding that alcohol exposure during fetal life kills neurons by programmed death (De et al., 1994). In a series of studies they have demonstrated that alcohol administration is harmful to the development and normal function of opioid neurons, which are critical for maintaining the body's stress response (Boyadjieva and Sarkar 1994; Boyadjieva et al 2002). Contributions of feasibility are related to the molecular mechanisms of alcoholisms. He showed that the administration of alcohol is not only harmful to the development and normal function of opioid neurons but is a significant cause of increased alcohol abuse. He also showed that alcohol promotes development of pituitary prolactin-secreting tumors. His group has also shown that Natural Killer (NK) cell functions, that help the body fight tumors, viruses, and bacteria, are governed by the body's clock machinery via the â-endorphin system (Arjona et al 2004; Arjona and Sarkar 2005). These studies may help in developing chronotherapy of human cancer. In addition they have also identified alcohol actions on clock-governing genes in the brain and lymphoid tissues (Boyadjieva et al 2004; Chen et al 2004).

The research of Dr. **Ratna Sircar**, from Albert Einstein College of Medicine, has resulted in better understanding of i) neuroadaptations following N-methyl-D-aspartate (NMDA) receptor channel blockade in the developing brain, ii) mechanisms underlying drug-induced cognitive deficits in the adolescent brain, and iii) psychopathology of schizophrenia. She and her colleagues have shown that postnatal phencyclidine (PCP) exposure causes long-term deficit in spatial memory in adult rats (Sircar, 2000). Her research contributes significantly to the formation of research strategies directed towards discovering the mechanisms underlying fetal PCP-induced brain damage and, since PCP is a potent NMDA channel blocker, it may also provide insights into the consequences of hypofunctioning glutamatergic system in the developing brain. The other area of Dr. Sircar's research is effect of adolescent drug exposure on brain and behavior. They have studied the short- as well as the long-term effects of adolescent alcohol exposure on spatial learning and memory. They have also been investigating the neurobehavioral consequences of ã-hydroxybutyric acid (GHB) in adolescent rats and have found that GHB exposure in adolescence rats, but not adult rats, has been associated with significant impairments in learning and memory (Sircar and Basak, 2004). The third area of Dr. Sircar's research involves patterns of gene expression in schizophrenia using cDNA microarrays. Using the microarray technology, they have identified several genes that are either upregulated or downregulated in the hippocampus of schizophrenics, and about two dozen genes that are upregulated in the prefrontal cortex region. They are continuing to identify these genes in a more detailed follow-up study.

Dr. **Lalit K. Srivastava** at the McGill University in Montreal, Canada, has focused his research program on understanding the neurobiology of schizophrenia though studies on animal models and to test the developmental hypothesis of

schizophrenia which posits that the disease arises from an anomalous development of the hippocampus that ultimately affects functioning of the neurotransmitter dopamine in the adult individuals (Laplante et al 2004; Flores et al 2005). Their studies showed that neonatally hippocampus-lesioned animals grow apparently normal until they reach puberty (Bhardwaj et al 2003). However, at that time the lesioned animals show a variety of cognitive, motor and social abnormalities, behaviors that have face validity with human schizophrenia. They also found that the post-pubertal, but not the pre-pubertal, lesioned animals also show morphological changes in the neurons of the prefrontal cortex in the form of reduced dendritic length and spine densities features that are again variously reported in postmortem schizophrenic brains (Laplante et al 2004).

The research of Dr. **Mriganka Sur** at MIT relates to cortical development plasticity and dynamics. Dr. Sur's research is focused on the field of cortical plasticity which is now recognized as one of the most remarkable brain feature in higher mammals, the cerebral cortex of the brain is the seat of highest mental abilities and connections between the cortical neurons are infringed by patterns of electrical activity during both development and in adulthood. Dr. Sur demonstrated the phenomenal capacity of the cortex to change adaptively under external inferences as it develops. He also showed how networks of the cortex create new properties from simple inputs and how these properties are dynamically modified in the adult brain by learning or by features of visual stimuli. He has also discovered specific mechanisms by which neuronal connections are sculpted by electric activity during brain development. More specifically, they examined the role of input activity in the development of cortical networks and functions by "rewiring" the brain (Sur et al., 1988) and showed that the auditory cortex is re-specified by vision: it develops a map of visual orientation and direction-selective cells (Roe et al., 1992) and a map of orientation-selective cells resembling the map in primary visual cortex (Sharma et al., 2000). In the area of plasticity in mature visual cortex, Dr. Sur has defined network mechanisms that lead to emergent responses in the visual cortex and the ways in which the responses can be dynamically altered in the adult brain. By recording intracellularly from single cells *in vivo* and *in vitro* and by concurrently blocking inhibition in individual neurons, he showed that orientation selectivity in visual cortex relied critically on summation of thalamic and cortical excitation (Nelson et al., 1994). His laboratory also developed a detailed computational model to propose that a key feature of cortical networks (i.e., local connections between excitatory neurons) is essential for explaining orientation selectivity (Somers et al., 1995). His laboratory has also contributed in clarifying the cellular mechanisms by which electrical activity influences neuronal growth and synaptic connections in the developing brain. Their research elucidated the sequence of signals by which electrical activity in inputs is transduced into patterns of synaptic connections in the visual thalamus and cortex. Dr. Sur laboratory uses an unusually rich variety of systems and techniques, several of which he has pioneered. These include single cell recording with multiple electrodes, intracellular *in vivo*, optical imaging of cortical

activity, confocal and two-photon imaging of cells and processes, DNA microarray and genomics analyses, focal gene insertion and deletion, anatomical and immunocytochemical labeling, behavioral methods and computational modeling.

Concluding Remarks

In this chapter we have attempted to highlight the research in neuroscience conducted by some of the Indian scientists in the USA. There are many more new scientists whose work has not been included but not by design. This is therefore an attempt to promote the vast areas of neuroscience research in which Indians are not only involved but are making significant contributions. It will be very much desirable to compile a list of Indian scientists in the USA with a short description of their research interests and contributions.

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