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International Symposium on Systems Biology in Physiology/Medicine

Abs.SB.1

Principles of Systems Biology

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I define systems biology as a theory of biological relativity in which the first principle is that there is no privileged level of causality (Noble, 2008, 2012). This is necessarily true in systems with multiple levels of feed forward and feedback. Genes, and proteins, do nothing on their own. There are multiple forms of 'downward' causation that 'play' the genome, with very different results in different cells, and in different circumstances. The term 'gene network' is therefore misleading. So is the idea of a genetic program. The central dogma of biology has been incorrectly interpreted (Noble, 2006; Shapiro, 2011). The full implications of epigenetic mechanisms have yet to be appreciated. I will illustrate the systems approach using successful simulation of the heart and its application in the development of new therapeutic drugs.

Noble D (2006) The Music of Life. OUP, Oxford.

Noble D (2008) Genes and Causation. Philosophical Transactions of the Royal Society A 366, 3001-3015.

Noble D (2012) A Theory of Biological Relativity: no privileged level of causation. Journal of the Royal Society Interface Focus 2, doi: 10.1098/rsfs.2011.0067.

Shapiro JA (2011) Evolution: a view from the 21st century. Pearson Education Inc, Upper Saddle River, NJ.

Abs.SB.2

Scale Relativity for Multi-Scale Integration in Systems Biology

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Systems approaches in biology are as old as physiology founded by William Harvey in the 17th century (Auffray and Noble Int. J. Mol. Sci. 2009, 10, 1658-1669). At a Nobel symposium held in Stockholm in 2002, I presented two conjectures for systems biology on stochasticity and biological space-time (Auffray et al. Phil. Trans. R. Soc. Lond. A 2003, 361:1125-1139): "We conjecture that biological systems self-organize because they operate as a conjunction between the relatively variable part of a stable organization and the relatively stable part of a chaotic network of fluctuations, and in a space with a changing number of dimensions: biological space-time." I will argue that complementing the four Cartesian precepts of objectivity, reductionism, causality and exhaustivity with the four systemic precepts of contextualisation, relatedness, conditionality and pertinence is a necessary condition for systems approaches to biological systems to succeed. The next question that arises in this context is the nature of the chaotic network of fluctuations in self-organizing systems. I will argue that the

chaotic network of fluctuations is an intrinsic and fundamental property in self-organizing systems, and that it is not simply "noise", but plays a key role in driving the behaviour of biological systems. Finally, I will discuss the extension of the principle of relativity to scales, as developed by Dr. Laurent Nottale, and how its associated mathematical tools can help formalizing biological space-time, help modeling and understanding biological systems, and resolve theoretically and practically the problem of integration across multiple scales and levels of organisation in biological systems, which is becoming a frontier challenge for the field (Auffray and Nottale, Progr Biophys Mol Biol 2008, 97:79-114; Nottale and Auffray Progr Biophys Mol Biol 2008, 97:115-157).

Abs.SB.3

Multi-Scale Structured Model for Analyzing Disease States in Metabolic Syndrome

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Despite the progress in various disciplines of Bio-medical research and availability of high-throughput techniques, we still are far away from the roots of various complex diseases. This puts forth a greater challenge to bring about a paradigm shift from the conventional ways of approaching complex systems. Systems biology is an emerging science that strives to fill this gap and synchronizes both the approaches to address the issues in biological systems. It tries to explore the inherent design principles of the biological systems which nature has engineered, and understand the mechanism of cause and effect. This approach has higher potential in biomedical research to study the functioning of human body from cellular to organ levels treating it as a whole operating system.

Metabolic syndrome is among the most complex diseases with multiple complications associated with it such as insulin resistance, central obesity, Type 2 diabetes, hypercholesterolemia, hypertension, atherosclerosis and coronary artery disease. It has been found that these are system level diseases with defects at metabolic, signaling and genetic levels rather than defects in individual biological entities. In metabolic syndrome, insulin resistance is the key defects which affect various metabolic processes. Defects in insulin secretion, its activity, and its signaling generate insulin resistance. Insulin signaling pathway orchestrate with various other pathways coupled with feedback mechanisms to generate the multiple desired effects. Moreover various other hormones and inflammatory pathways are known to modulate the insulin activity. Insulin resistance is the combinatorial effect of all these factors.

The systems biological approach with mathematical modeling of the biological networks serves as an important way to assess these diseases. We attempt to integrate the models of meal simulation, whole body metabolism, insulin signaling pathway and insulin secretion which scale from cellular to organ levels. We resort to the kinetic modeling and analysis of the integrated network and analyze the metabolic response with respect

to perturbation in various parameters of the model. Parameter values and other constants are collected from the literature and are also estimated through optimization and curve fitting for the model. The models are then simulated for sensitivity and phase-plane analysis to notice the key parameters that have major influence on the overall network behavior. Furthermore, perturbation analysis is performed to get the matrix of parameters for healthy and disease phenotype. Such an analysis helps in understanding the system dynamics and help in answering various 'What-if' kinds of questions that can aid in identification of potential drug targets and design effective therapies.

Abs.SB.4

The Physiome Projects: Modeling toward Human Health

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As biological science deepens, integrative models of biological systems become of central importance in identifying and organizing the current knowledge and aiding the planning of experimental studies to make the next discoveries. The ease of understanding models however diminishes as the complexity increases, necessitating better interfaces and broader tutorials and operational instructions. Modular construction favors identifiability of elements and the understanding of components. With new methods one can automate the reconstruction of large models when components are modified or new ones added. The modularity thereby fosters international collaboration in building and updating comprehensive models. Eventually these models will become powerful enough to provide and understanding of multigenic disorders.

Such models summarize and epitomize the results of sometimes thousands of experiments, even though data sets are commonly incomplete. The storage and retrieval of anatomic, physiological and pathological data and images is far more complicated than for genomic and proteomic data, but now is the time to develop national and internationally supported databases to facilitate building the models on the basis of accurate data. The combination of good data and the evaluation of comprehensive, self consistent, quantitative models will put evidence-based medicine on a solid footing.

Abs.SB.5

Understanding Endometrial Receptivity for Blastocyst Implantation using a Systems Biology Approach

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Time-synchronous development of endometrium and embryo under adequate hormonal regulation is considered integral to the process of blastocyst implantation in the human. Although several lines of evidence substantively corroborate the paradigm, several studies in past failed to align with it. It now appears that hypothesis-driven and candidate-based deductive approach fails to explain the complex control process of

endometrial receptivity toward blastocyst implantation. In the present study, we propose to forward a systems biology approach to elucidate the control process underlying the physiological basis of successful interfacing between embryo and endometrium towards blastocyst implantation. Accordingly, a systems biology model of a hierarchical arrangement of functional networks of regulatory genomic expressional elements at several levels shall be put forward. The existence of functionally connected genes in controlling the process of endometrial receptivity to blastocyst implantation in the mid-luteal phase endometrium with and without progesterone dominance, as well as, with and without viable embryo shall elaborate upon the polygenic nature of the process of endometrial receptivity and blastocyst implantation. It is anticipated that a systems biology approach, in one hand, shall provide both telescopic as well as microscopic pictures of the process and, on the other hand, shall open up novel areas of basic, strategic and translational research in the biology of embryo implantation. Supported by WHO-Rockefeller Foundation and DST.

Abs.SB.6

Pharmacogenomics of Cardiovascular Drugs: Integration of Genomics, Transcriptomics and Biomarkers for a Systems Biology Approach

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Personalized medicine is based on a better knowledge of biological variability between individuals, considering the important part due to genetics, without neglecting environmental influences. Pharmacogenomics and pharmacoproteomics approaches of many cardiovascular drugs are very often essentially looking to the pharmacokinetic step with the main CYP involved in the oxidation of the drugs and the ABC transporters. But the majority of these enzymes and systems are membranous, localized in the endoplasmic reticulum and are rarely released into blood or plasma. Fortunately, blood carries cellular and non-cellular components that could be use.

WBC might be useful to follow through a transcriptomic approach the gene products of many drug metabolizing enzymes including the following CYP: 1A1, 1A2, 1B1, 2A6, 2B6, 2C, 2D6, 2E1, 3A3, 4B1, 4F. Phase III transporters i.e. the ABC genes also expressed in lymphocytes could be surrogate markers for testing individual responses to cardiovascular risks factors or to cardiovascular drugs such as statins or fibrates. We should not forget to look simultaneously to the transcription factors present in WBC, particularly Ah receptor, other nuclear factors (RXR, CXR, PPAR) which are regulating the expression of drug metabolizing enzymes.

We will attempt to review the situation of all these enzymes and genes in prevision to their use in pharmacogenomics and to describe the biological variations of some messenger RNAs. Drug metabolizing enzymes not only can oxidize and hydrolyze drugs but also participate in endobiotics natural substrates metabolism. They act on endogenous arachidonic acid catalyzing its conversion into

epoxy-eicosatrienoic acids (EETs). The epoxide ring of these EETs may be cleaved by the action of epoxide hydrolases to yield the corresponding vicinal diols.

Our study of the expression of CYP 2C,8,9,18,19 and CYP 2J2 genes in vascular tissues demonstrated that they are differently expressed in healthy and varicose veins.

In order to examine the potential relationship between the anti-inflammatory properties of EETs and the expression of cytochromes P450, we studied the expression of cyps in the Apo E-/- mouse model. These experiments revealed a significant increase of cyp 2j5, the mouse homologue of CYP 2J2, and cyp 2c in the arterial wall of this animal model and more after LPS treatment.

Next, we investigated the relation between CYP 2C19 polymorphisms in a sample of volunteers selected from the STANISLAS Cohort. The isoforms of these enzymes showed differential activities which is due to genetic polymorphisms within CYP 2J2 and CYP 2C19 genes (deletions giving inactive enzymes).

We genotyped 300 subjects from the STANISLAS Cohort and in the non active CYP 2C19 group the levels of TNFá, IL6 and CRP were increased, suggesting a possible link between the decreased CYP 2C19 activity. It should then be possible to target these enzymes and epoxyde hydrolase for modulating inflammation related disorders.

In conclusion, integrating genetic data, transcriptomic and protein ones, is the strategy for developing pharmacogenomics for personalizing the treatment and avoiding side effects and drugs interactions. This is typically a systems biology approach.

Abs.SB.7

Synthesis of Systems Level Gene Expression and Genetic Analyses in Epilepsy

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Not clearly understood in cellular and molecular terms, epileptogenesis, i.e., development of epilepsy, is a network problem involving molecular, structural, and functional alterations in the brain. A systems level understanding of epileptogenesis is expected to facilitate development of novel anti-epileptogenic, disease-modifying, and neuroprotective agents. Unbiased genome-wide expression analysis offers a promising approach to identify relevant pathways underlying the pathopysiological mechanisms. The available expression data related to human epilepsy and animal models of epileptogenesis differs with respect to the use of brain regions, methods to trigger epileptogenesis, tissue sampling time-points, epilepsy phenotype assessment, animal species and strains etc. Results of these individual studies do not compare well with each other possibly because of these differences. Considering that synthesis of the expression data may however still be possible, a convergent analysis of genome level expression studies in epilepsy will be presented. The genes and pathways identified through this convergent approach will be further examined in view of the existing genetic, chemogenomic, cellular and molecular evidence in epilepsy. The point will be made

that synthesis of diverse genome level expression analysis may potentially uncover the mechanisms underlying complex brain disorders.

Abs.SB.8

Exploiting Host-Factor Dependencies: An Alternate Approach to Drug Target Discovery

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The vast majority of pathogens of the human hosts have co-evolved along with the host so as to be able to successfully infect the target cells, and survive in them. They are able to do so by adapting to the intracellular milieu through complex interplay with host cell machinery. This host-pathogen interplay manifests at every level of cellular regulatory machinery including signaling network, metabolic network and transcriptional regulatory network. Pathogen-derived molecules tend to co-opt these regulatory modules and influence them in a manner that facilitates their survival within the host cell. This is especially true of Mycobacterrium tuberculosis (Mtb), which has evolved elaborate strategies to survive within the endocytic vesicles of human macrophages. Subversion of the host cell by the microbe has been shown to be mediated through interactions with proteins secreted by the intracellular pathogen. Our thesis, therefore, is that an approach that can disrupt the key molecular interactions that promote this adaptation may provide an alternate strategy for chemotherapy. To explore this, we have adopted a two-phase strategy where the first phase involves the generation of a complete 'parts list' of the host cell regulatory molecules that are either targeted or influenced by the pathogen. For this, we are currently performing a genome-wide siRNA screen of human macrophages infected with Mtb. This information obtained from this screen is also being employed to identify the molecular axis that is involved in regulating pathogen survival. It is our hypothesis that the components of such an axis will also serve as a list of candidate targets for the development of chemotherapeutic strategies aimed at disabling the adaptive mechanisms of the pathogen. Thus our present approach seeks to extend systems biology, towards a translation-oriented exercise that could perhaps be termed as 'systems pharmacology.' The talk will focus on the progress made in these experiments, as well as elaborate on the novel concepts emerging from this screening exercise.

Abs.SB.9

In Search for the Regulatory Network of Aging

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Many fundamental questions on aging are still unanswered or are under intense debate. These questions are frequently not addressable by examining a single gene or a single pathway, but can best be addressed at the systems level. Previously we have examined

the modular structure of the protein–protein interaction (PPI) networks during fruitfly and human brain aging. We found that in both networks, there are two modules associated with the cellular proliferation to differentiation temporal switch that display opposite aging-related changes in expression. Recently, we started to examine not only age-dependent transcriptomic changes, but also gene expression changes in the mouse liver under different dietary conditions which result in different life-spans and aging-related phenotypes in the liver. This allowed us to identify genes and pathways that modulate the aging process through dietary intervention. In addition to examining transcriptomic changes, we also explored the epigenetic changes during the aging process in C. elegans and Rhesus macaque using ChIP-seq, and identified key epigenetic events modulating the aging process.

Abs.SB(PD).1

Synthesis of Robust Biochemical Networks: An Algebraic Approach

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The design methodology of a class of synthetic biochemical networks will be presented in this paper. A set of sufficient conditions has been derived for analysing the robustness of nonlinear biochemical network at its steady-state condition. These sufficient conditions are formulated as linear matrix inequalities (LMIs) in the framework of computationally attractive convex optimization problems. The synthetic system becomes robust in terms of its sensitivity to both intrinsic and extrinsic perturbations. An upper bound of this perturbation sensitivity has been derived for the synthetic system. This upper bound has been minimized for enhanced robustness to parameter perturbations. A constrained class of robust synthetic networks has been designed preserving the structural topology of the biochemical networks.

Abs.SB(PD).2

NeuroDNet: a Database for Constructing and Analyzing Neurodegenerative Disease Networks

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Neurodegenerative disorders (NDDs) are caused by aberration in the genetic circuitry that controls the normal function in neuronal cells. The aberration may arise, for example, from a mutation of a gene leading to a loss of functional protein or a severe stress condition resulting in an irreversible change in regulation. The large number of signaling molecules, genes and proteins, and complexity of the network circuitry involved has discouraged probing of molecular mechanism that underlie neuronal deterioration. The challenge lies in the development of a theoretical framework that will enable the organization of existing data, and permit the interrogation and interpretation of mechanisms causing disease. To address these issues, we have created a database, NeuroDNet, that brings together under one

portal the information about the genes, proteins, signaling molecules and their interaction, associated with neurodegenerative diseases. It has a three-tier architecture - foundation, function and interface. The foundation table contains the human genome data and the list of genes associated with the neurodegenerative diseases reported in clinical studies. Data for the other tiers were curated from OMIM, NCBI, UniProt, GeneOntology, Cell Signalling, KEGG, BioCarta, Reactome, HPRD, BioGrid, MINT and DIP. These tiers are linked through functional features. The current version of the database integrates five neurodegenerative diseases. It contains 23857 protein-coding genes and 380 risk alleles for neurodegenerative diseases. Using the features offered by the NeuroDNet portal, interaction networks can be created and analyzed with Boolean and differential equation formalisms. The performance of the NeuroDNet for three case studies will be presented. NeuroDNet is freely accessible at http://bioschool.iitd.ac.in/NeuroDNet/.

Abs.SB(PD).3

Systems Biology to Understand Host-Pathogen Interactions

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Discovery of antibiotics more than half a century ago had raised the belief that era of infectious diseases could be well over. Several decades afterwards, infectious diseases are still a cause of major health concern, rather in a more alarming state-what with evolution of various multi- and extensively drug resistant strains. Consequently, we are forced to reconsider the approaches that have been adopted for targeting infectious diseases. Multi-target therapy however remains at the core of novel strategies. Though not a new concept as such, recent developments have paved ways for identifying heterogeneous targets for the multi-target therapy. In this context, reliance of infectious agents on host cellular factors have particularly come under extensive scrutiny, bearing on the fact that host factors play a crucial role throughout the etiology of diseases. The identification of these factors could however be a difficult task given the complex nature of the host-pathogen dynamics.

Recently utility of systems level approaches for addressing these and related concerns have been highlighted through studies based on genome-wide screening, proteomic and transcriptomic analyses. We will discuss how combining these systems level approaches together could help us understand various infectious disease biology and identifying novel approaches for their management.

Plenary Lecture

Abs.PS

Physiology and Evolution

Denis Noble

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Gene-centric interpretations of evolution, and more particularly the selfish gene expression of those interpretations, form barriers to the integration of physiological science with evolutionary theory (Noble, 2011b). A gene-centred approach analyses the relationships between genotypes and phenotypes in terms of *differences* (change the genotype and observe changes in phenotype). We now know that, most frequently, this does not correctly reveal the relationships because of extensive buffering by robust networks of interactions. By contrast, understanding biological function through physiological analysis requires an *integrative* approach (Noble, 2011a) in which the activity of the proteins and RNAs formed from each DNA template is analysed in networks of interactions (Kohl *et al.*, 2010). These networks also include components that are not specified by nuclear DNA. Inheritance is not through DNA sequences alone (Gissis & Jablonka, 2011). The Modern Synthesis therefore needs to be extended or replaced (Pigliucci & Müller, 2010; Shapiro, 2011).

Gissis SB & Jablonka E, ed. (2011). Transformations of Lamarckism. From Subtle Fluids to Molecular Biology. MIT Press, Cambridge, Mass.

Kohl P, Crampin E, Quinn TA & Noble D. (2010). Systems Biology: an approach. Clinical Pharmacology and Therapeutics **88,** 25-33.

Noble D. (2011a). Differential and integral views of genetics in computational systems biology. Journal of the Royal Society Interface Focus **1,** 7-15.

Noble D. (2011b). Neo-Darwinism, the Modern Synthesis, and Selfish Genes: are they of use in physiology? Journal of Physiology **589,** 1007-1015.

Pigliucci M & Müller GB, ed. (2010). Evolution - The extended synthesis. MIT Press, Cambridge, Mass.

Shapiro JA. (2011). Evolution: a view from the 21st century. Pearson Education Inc, Upper Saddle River, NJ.

Symposium 1 (S1)

Abs.S1.1

Health Issues Relating to Glutamate Use in the Diet

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Claims of adverse effects of monosodium glutamate (MSG) emerged in the 1960s.The main claims were that MSG caused (a) Chinese Restaurant Syndrome (CRS), characterized as neck numbness, general weakness and palpitation, and (b) a toxic effect in brain, infants being most susceptible. Other claims have surfaced since. Much research was subsequently conducted in animals and humans, which led regulatory bodies to conclude that MSG is safe in the food supply. Nonetheless, the question of MSG safety occasionally resurfaces. The issues are: (1) CRS, (2) neurotoxicity in brain, (3) obesity, and (4) hypertension. For CRS, a careful study of supposedly MSG-sensitive subjects showed that no one gets consistent, reproducible reactions to MSG that qualify as

CRS. For brain neurotoxicity, the key mechanism advanced was MSG penetration from the gut into blood and then brain, where it caused neuronal overexcitation and death, and brain dysfunction. Numerous studies have shown that MSG ingestion does not push glutamate into brain at any age. Hence, neurotoxicity does not occur when MSG is ingested. Obesity has recently been claimed to be caused by MSG ingestion, based on epidemiologic findings. However, controlled studies in animals do not find that dietary MSG induces weight gain. Finally, a recent epidemiologic study reports a weak, positive association between MSG intake and blood pressure. However, studies in animals and humans given MSG orally in large doses have not found hypertensive effects. In sum, the extensive experimental literature in animals and humans supports the conclusion that MSG is safe in the human diet.

Abs.S1.2

Multiple Receptor Systems for Umami Taste Perception in Humans and Mice

Yuzo Ninomiya*, Ryusuke Yoshida, Keisuke Sanematsu, Keiko Yasumatsu, Noriatsu Shigemura

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Umami, first described by K. Ikeda about a century ago, is the characteristic taste sensation elicited by the sodium salt of the amino acid glutamate (MSG) and 5'-ribonucleotides such as IMP (inositol monophosphate) and GMP (guanidine monophosphate). When added to many foods, these umami substances enhance their palatability. Studies using a variety of approaches have indicated that the umami taste is unique, that is distinct from the tastes of sweet, bitter, sour and salty, and play a key role in intake of amino acids. Recent molecular biological studies have identified strong candidates for umami receptors, including the heterodimer T1R1+T1R3, and truncated type 1 and 4 metabotropic glutamate receptors missing most of the N-terminal extracellular domain (taste-mGluR4 and truncated-mGluR1) and brain-mGluR1 and brain-mGluR4. The finding that human T1R1+T1R3 heterologously expressed in human embryonic kidney cells preferentially responds to glutamate, provides strong molecular evidence for specific umami detection in humans. Multiple lines of evidence argue for the involvement of T1R1+T1R3 in umami responses of both humans and mice. Although several studies argue for the involvement of receptors other than T1R1+T1R3 in umami, the identity of those receptors remains unclear.

We have recently investigated potential contribution of these candidate receptors for umami taste responses in human genetic and mouse molecular and electrophysiological studies. The results indicate that there is a strong association between recognition thresholds for umami substances and genetic variations in human TAS1R1, TAS1R3 and GRM1 (mGluR1). In mice, taste cells and nerve fibers that respond to umami compounds are classified into multiple types based on their susceptibilities to specific inhibitors and antagonists for T1R1+T1R3 and mGluRs. These data provide further evidence for the involvement of mGluRs in addition to T1R1+T1R3 in human umami perception and mouse umami taste responses.

Abs.S1.3

Brain-Taste-Gut Communication of Glutamate Signaling during and after Mealing

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Gustatory and visceral stimulation of food regulates digestion and absorbed nutrient utilization. Free glutamate (Glu) release from food induces the umami taste that increases food palatability. Dietary glutamate is the main source of energy for the intestinal mucosal absorption and metabolism, thus, only a trace amount of Glu reaches the general circulation even after the intake of dietary protein and Glu added in foods when umami taste sensation is not sufficient to be palatable. In addition to these roles, we demonstrated a unique gastric sensing system for Glu. Glu is the only amino acid that activates rat gastric vagal afferents from the luminal side possibly via metabotropic Glu receptors on mucosal cells. Functional MRI (4.7T) analysis revealed that luminal sensing with 1% Glu (most preferred concentration) in rat stomach activates the medial preoptic area (body temperature control) and the dorsomedial hypothalamus (basic metabolic regulator), resulting in diet-induced thermogenesis without changes in food intake. Interestingly, rats fed a high fat and high sugar diet with free access to 1% Glu and water showed the strong preference for Glu solution, and subsequently lower fat deposition, weight gain and blood leptin compared with those without Glu. In addition, these brain functional changes were abolished in the case of total vagotomized rats. Total and partial gastric and celiac branches vagotomy induced similar results to each other, suggesting that glutamate signaling should be yielded from the luminal side of the alimentary tract to contribute to the maintenance of our healthy dietary life.

Abs.S1.4

Flavor Perception, Imprinting, and Infant Growth

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Many of the most common human health problems are related to the amounts and kinds of food eaten. Since the flavor senses, mainly taste and smell, play a central role in determining food choice, an understanding of the factors that determine human flavor preferences is critical if we are to develop strategies to diagnose, treat and ultimately prevent these nutritionally related diseases. Some taste preferences and aversions are innately organized although early experiences can modify their expression. Both before and after birth humans are exposed to a bewildering variety of flavors that can influence subsequent liking and choice. We have been studying as a model system flavor learning in infants that are fed formulas containing hydrolyzed casein as their amino acid source. To adults these formulas are extremely unpalatable but very young infants accept them readily. We have discovered a sensitive period when exposure to these flavors renders them highly palatable – possibly for the rest of their lives.

Interestingly, these formulas are very high in free glutamate and in this regard resemble human milk. In very recent studies, we found that infants fed these casein hydrolyzed formulas grow at a rate that resembles the optimal rate for the breast fed infant whereas infants fed regular cow milk formulas grow faster and, according to some studies, are more prone to later obesity. We are currently entertaining the hypothesis that the hydrolyzed protein formulas are more satiating than unhydrolyzed cow milk formula and that the agent(s) mediating this satiation effect may be free amino acids, perhaps including glutamate.

Symposium 2 (S2)

Abs.S2.1

Sertoli-Germ Cell Interactions in Initiation of Spermatogenesis

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Testicular Sertoli cells (Sc) have a crucial role in the initiation and maintenance of spermatogenesis. Although circulating levels of LH, FSH and testosterone (T) in infant monkeys (< 4 months-old) and boys (< 6 months old) are similar to that found during puberty, Sc fails to support spermatogenesis during infancy. Xenografting studies have shown that infant germ cells are quite capable of undergoing differentiation when grafted in conducive environment, suggesting that functions of infant Sc are suboptimal or defective during infancy. Lack of spermatogenesis in the phase of high hormones during infancy is a situation similar to that found in certain categories of male infertility. To investigate this intriguing situation, Sc were isolated and cultured from various age groups of monkeys. Androgen receptor (AR) and FSH receptor (FSHR) signaling in Sertoli cells (Sc) isolated from testes of infant monkeys were compared with those in Sc from spermatogenically active testes of pubertal monkeys. Although AR and FSHR mRNA expressions were comparable at these two stages of development, androgen binding ability of AR and FSH mediated cAMP production by Sc were extremely low during infancy. Testosterone (T) and FSH failed to augment the expression of T responsive gene, claudin11, and FSH responsive genes, inhibin-B, stem cell factor (SCF) and Glial cell line derived neurotrophic factor (GDNF) by infant Sc. However, intracellular stimulation of FSHR by cholera toxin (CT) augmented cAMP production in infant Sc. Similarly in rats, infancy is associated with sufficient circulating hormones but lack of spermatogenesis. Rat Sc studies suggested that AR activity is limited in neonatal life but improves with Sc maturity after 12-days of age whereas, responsiveness of Sc towards FSH changes in between 9 to 12-days of age due to improved binding of FSH to FSH-R. From these observations, we believe that compromised AR and FSHR mediated signaling in infant Sc might be responsible for the azoospermia in the infantile testes in spite of adequate hormonal milieu, a situation similar to that in certain forms of idiopathic male infertility. With the help of available tools, age specific genes expressed by the Sc from infant and pubertal monkey and rat Sc are also being examined to find their correlation with the status of germ cell development in the testis.

Abs.S2.2

Modulation of Gonadal Development through Circadian Oscillations

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Reproductive cycle generally seems to be synchronized with external and internal factors such as photoperiod, availability of food, favorable conditions, neural inputs, hormonal balance etc. Neural, endocrine, biochemical and behavioral rhythms provide the basis for temporal organization of reproductive functions which also involve temporal synchronization of reproductive events within the population as well as between the individual and the external environment. Effects of all the external and/ or internal factors regulating reproduction are funneled through hypothalamo-hypophyseal-gonadal axis. A large number of studies from our laboratory have reported that the circadian phase relation of serotonergic and dopaminergic oscillations may regulate seasonality such as reproduction (HPG axis), fattening, hormonal changes in seasonally breeding birds and mammals. Moreover, a possible role of circadian organization has also been observed in the puberty attainment of an avian (Japanese quail) and a mammalian (mice) model. In a specific protocol serotonergic and dopaminergic precursor drugs 5-hydroxytryptophan (5-HTP) and 3, 4-dihydroxy-L-phenylalanine (L-DOPA) were injected intra-peritoneally (5mg/100gm body weight) at specific time interval (0, 4, 8, 12, 16 or 20 hr) over a period of 11-13 days. This set of treatment induced long term effect on the reproductive performance of the species tested so far. In general 8-hr relation suppresses and 12-hr relation of these drugs stimulates gonadal growth, development and fertility in seasonally breeding species. These findings indicate the importance of temporal synergism of neural oscillations in the reproductive regulation (both puberty attainment and fertility/ sterility) of different species through neuroendocrine axis and suggest the role of circadian organization in body physiology.

Abs.S2.3

Sperm DNA Damage and Transgenerational Changes in Genomic Instability

Satish Kumar Adiga

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Male factor infertility remains a significant problem contributing approximately 40% of cases attending infertility clinics. In many infertile men, the standard laboratory analysis of the semen reveals no detectable abnormality and therefore, the couple is diagnosed with unexplained or idiopathic infertility. Sperm DNA integrity is necessary for accurate transmission of genetic information to the offspring. There is now clinical evidence to show that damage to human sperm DNA may adversely affect reproductive outcomes and that spermatozoa of infertile men possess substantially more DNA damage than do spermatozoa of fertile men. The germ-line instability caused by various environmental agents and occupational factors is able to persist in populations for

several generations and this instability would lead to a significant increase in mutation load. Using mouse model we reported a hierarchy in damage response in preimplantation embryo derived from the DNA damaged sperm. In addition, the implantation potential of the embryos derived from the DNA damaged sperm was reduced and the feto-placental ratio was altered in relation to the extent of sperm DNA damage. The genetic instability is equally elevated in the germ line and somatic tissues of first generation (F1) offspring suggests that implantation and post implantation developmental competence of the embryos and the genomic instability are compromised in relation to sperm DNA damage load.

Abs.S2.4

Chromium and Vanadium Induced Testicular Toxicity

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Gonadal disruption under the influence of environmental pollutants is of current interest in reproduction. The objective of the study was to evaluate the physiology of testicular disruption under exposure of chromium and vanadium respectively in an animal model, to study its mode of action and possible prevention. The study was conducted in adult Sprague Dawley rats after exposure of chromium and vanadium respectively at sub-lethal doses with different concentrations for different durations. The parameters studied were morphology and histology of testis, accessory organs, sperm count followed by assay of the activities of steroidogenic enzymes viz. Δ^5-3β HSD and 17β HSD, assay of hormonal profiles viz. FSH, LH and testosterone for the evaluation of testicular degeneration. Possible mode of action investigated through generation of oxidative stress by LPO, SOD and Catalase in testis. Subsequently, prevention was assayed after supplementing Vitamin C, E, zinc-chelator and curcumin including testosterone therapy. The results revealed that the morphology, histology and even the epididymal sperm count were significantly altered after exposure to these heavy metals depending on dose and duration. Biochemical observations showed marked alteration in the activities of steroidogenic enzyme and alteration of hormonal profile developing a hypogonadal state. Decreased SOD and Catalase activities followed by enhanced LPO were noted in the treated animals compared to control while testicular morphological, histological and histometric parameters, testicular stress enzymes status remained almost unaltered in treated animals which were simultaneously supplemented with antioxidants. Sublethal doses of these heavy metals results in testicular disruption depending on the dose and the duration of their exposure that generated oxidative stress. However, simultaneous antioxidant supplementation may prevent the disruption.

Abs.S2.5

Cellular and Molecular Regulation of Blastocyst Hatching

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In mammals, including humans, blastocyst hatching and implantation failures lead to early embryonic loss and infertility. Prior to implantation, the blastocyst must hatch out of the acellular glycoprotein coat i.e. zone pellucid (ZP) of the preimplantation embryo. The phenomenon of blastocyst hatching is believed to be regulated by a variety of molecules such as growth factors, cytokines and proteases. Moreover, dynamic cellular components such as trophectodermal projections (TEPs) appear to be involved in hatching (Seshagiri et al., 2002; Sireesha et al., 2008). We have been keenly investigation the spatio-temporal regulation of zonalysis during the peri-hatching development by blastocyst derived-cellular and molecular factors. Our functional studies show that blastocyst hatching, in the golden hamster, is accelerated by growth factors i.e., heparin binding epidermal growth factor or leukemia inhibitory factor. Using a range of protease inhibitors of the three classes of cysteine proteases, we show that embryo-derived, cysteine protease(s) i.e., cathepsisns are potentially responsible for zonalysis during blastocyst hatching. Moreover, inhibition of the inducible enzyme cyclooxygenase (COX-2) and the estrogen receptor (ER)-á in cultured embryos result in impaired hatching. We also show that during the peri-hatching development, blastocysts exhibit extensive actin-based TEPs, which are intimately involved with lysing ZP. Interestingly, TEPs enrich and harbor a few of the above described key hatching-enabling factors viz., cathepsins (-L and -P) and their potential regulators: COX-2, ER-á and NFkB. Taken together, we show that blastocyst-derived cathepsins and TEPs and the associated signaling biomolecules are functionally involved in hatching. These observations provide new insights into our understanding of the phenomenon of mammalian blastocyst hatching (Support: DST, New Delhi).

Abs.S2.6

Maternal Fetal Interaction in the ABO Blood Group System: A Study on Fetal Wastage in a Bengalee Population

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The selective effects on genotypes could be perceived by its manifestation in pre zygotic and post zygotic stages which may be extendable to neonatal and post natal periods. Selective elimination of genotypes could generally be understood by the study of reproductive performance of the couple on the basis of mating types. Actual studies on products of conception of these couples essential for understanding the process of selective elimination of the alleles. Selection adjudicated by relative fitness of the genotypes determines their incidence in the next generation. The present study comprised of 992 abortive parents, 124 spontaneous aborted foeti and 1000 newborns along with their 1814 parents. The result of the present study indicated significantly ($p<0.05$) higher frequency of ABO incompatibility among the couple having spontaneous abortions in comparison with the couple combination of the parents of the newborns. Furthermore, significant heterogeneity has been found in the distributions of ABO blood group alleles

between the couple having spontaneous abortions compare to the couple of the newborns. However, significantly ($P<0.05$) higher A alleles revealed among the fetus compare to the newborns. Therefore the present study vindicated ABO incompatibility between the couples is likely to be a risk factor for early spontaneous abortions and also the heterozygote selection of ABO blood group genotypes.

Abs.S2.7

Role of Gene-Environment Interaction in Adverse Reproductive Outcomes

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Many human disorders result from a complex interaction between an individual's genetic make-up and environmental stressors Humans are exposed to numerous xenobiotics constantly and unavoidably such as pesticides, metals, PCBs etc. Endocrine disruption, genetic predisposition, altered immune surveillance, inflammation and subsequent oxidative stress may antedate adverse reproductive outcomes and contribute to its pathogenesis. Although environmental factors are important, genetics clearly plays a role in adverse reproductive outcomes. Identification of genetic susceptibility variants will lead to better understanding of the role of variable factors in adverse reproductive outcomes. It has been observed that a lot of women with genetic polymorphism do experience normal delivery while some do not. It can be hypothesized that genetic polymorphism requires the presence of certain environmental stimuli to have consequences of clinical significance. The recent abundance of epidemiologic research examining associations between polymorphic genes that code for enzymes involved in xenobiotic biotransformation and disease has on occasion generated interesting findings. Recent studies from our laboratory clearly showed the importance to assess the role of variations in the human genome (polymorphisms) in modifying the effect of exposures to xenobiotics to define "Gene–Environment Interaction", which render some individuals or groups in the population more or less likely to develop adverse health effect. Current and future efforts to identify new polymorphisms in genes involved in environmental response with larger sample size will broaden the scope of potential genetic effect modifiers. Currently, our laboratory is involved in studying the role of "Gene-Environment Interaction" with reference to xenobiotic metabolism and oxidative stress related genes in various diseases such as cancer, neurodegenerative diseases, chronic kidney disease, hypospadias and we have reported the association of organochlorine pesticides (OCPs) with many of adverse reproductive outcomes such as preterm birth, intrauterine growth retardation, recurrent miscarriage. Our effort in this area may also lead to the development of possible biomarker(s) to screen individuals, exposed to pesticides and preventive measures for safe reproductive outcomes. Determining the effect of these polymorphisms along with OCPs burden will be of paramount importance in an early diagnostic strategy and preventive measures for adverse reproductive outcomes

with reference to environmental toxins.

Abs.S2.8

Antimicrobial Peptides and Early Placentation

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Antimicrobial peptides are fast emerging as alternative to conventional antibiotics to which various bacterial strains are increasingly showing resistance. Antimicrobial peptides known as host defense peptides form an evolutionarily conserved component of innate immune response. In this category the gene encoded cationic antimicrobial peptides preferentially interact with negatively charged lipids, which are major components of bacterial cell membranes resulting in membrane perturbations such as pore formation, alterations of the curvature strain and induction of lipid-peptide domain formation resulting in membrane dysfunction. In mammalian cell membranes, negatively charged moiety such as phosphatidylserine (PS) line inner cell membranes with the exception that in the placenta the PS flip and its externalization involves syncytialization. Placental growth in the first trimester is exponential and is derived from the progenitor population of cytotrophoblast cells. Cytotrophoblast cells differentiate into intermediate type or transitional type of cytotrophoblasts that undergo fusion to form the multinucleated outer layer of syncytiotrophoblast. Therefore we undertook a study to examine the potential toxicity if any of first trimester placental cytotrophoblast cells to an in vitro exposure to a synthetic AMP, Ala8,13,18-magainin II amide (AMA). Administration of AMA resulted in attenuation of differentiation, enhancement in apoptosis and loss of viability in early placental villi trophoblast cells in primary culture. It appears that administration of alpha-helical AMP may adversely affect the process of placentation and pregnancy outcome.

Abs. S2.9

Trophoblast and Fusion

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In the human placenta, the chorionic villi are covered by a two-layered epithelial layer, the villous trophoblast. Mononucleated stem cells resting on the basement membrane, the villous cytotrophoblast, proliferate, leave the cell cycle and start to differentiate. Their final differentiation step is syncytial fusion with the second layer, the multinucleated syncytiotrophoblast. Villous cytotrophoblast differentiation and fusion with the overlying syncytiotrophoblast is regulated by factors such as growth factors, cytokines, transcription factors, structural membrane proteins and proteases. Differentiation and subsequent fusion of villous cytotrophoblast with the overlying syncytiotrophoblast is an essential process for growth and maintenance of the villous trophoblast layer in the human placenta. The understanding of intrinsic mechanisms behind this process is in its infancy, while the list of suggested factors, involved in intercellular fusion of villous

trophoblast, rapidly increased in the recent past and promises progress on this issue. The early stages of the apoptosis cascade, in particular caspase 8, was suggested to trigger differentiation of the cytotrophoblast, priming them for upcoming fusion. This may sound paradoxical, especially for those who still associate caspase activity with apoptosis only. During the last decade we have shown evidence that activity of apoptosis related mechanisms is a prerequisite for the process of syncytial fusion. Especially, caspase 8, an aspartate-specific cysteine protease, also known as one of the initiator caspases during apoptosis, has been shown to be crucial for villous trophoblast differentiation. It is hypothesized that caspase 8 is activated in villous cytotrophoblast just prior to fusion of these cells and escorts the nuclei from the mononucleated to the syncytial state. Here, data on caspase 8 in the villous trophoblast layer will be summarized, with a specific focus on localization of pro and active forms, the sites of its activation and deactivation, and its role and regulation during fusion.

Symposium 3 (S3)

Abs.S3.1

Role of Adenosine in the Regulation of Sleep during Hypobaric Hypoxia

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Objective : Sleep disturbance in hypobaric hypoxia and role of brain monoamines is being investigated by this laboratory. The present study aimed to investigate the role of another neurotransmitter adenosine and its receptor subtype in sleep in continuous hypobaric hypoxia.

Method : Rats were exposed to simulated altitude ~ 7620 m(282mm Hg, partial pressure of O2 59 mmHg) for 7 and 14 days continuously in an animal decompression chamber. During the period of hypoxia exposure, adenosine A1 receptor agonist and antagonist were injected intraperitoneally and sleep was recorded after 7 and 14 days of exposure. Rats were sacrificed and brain adenosine levels were estimated by HPLC.

Results : After administration of adenosine A1 agonist, quiet awake stage was significantly decreased ($P<0.05$) and quiet sleep, deep sleep and REM sleep stages and total sleep time significantly increased ($P<0.05$). After administration of A1 antagonist quiet awake increased ($P<0.01$), while deep sleep and total sleep time decreased ($P<0.01$),with no significant change in REM sleep and quiet sleep stages. Brain adenosine level significantly increased after 7 ($P<0.05$) and 14 days ($P<0.01$) of hypoxic exposure.

Conclusion : Changes in total sleep time and different sleep stages by adenosine A1 receptor agonist and antagonist point to a modulatory role of adenosine in hypobaric hypoxia.

Abs.S3.2

High Altitude Physiology: Neural Basis of Hypobaric Hypoxia Induced Cognitive Deficits

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Hypobaric hypoxia (HBH) encountered at high altitude is known to have deleterious effects on cognitive functions. Individuals exposed to HBH commonly confronted with problems such as acute mountain sickness, high altitude pulmonary and cerebral edema. Simulated hypobaric hypoxia (HBH), resembling high altitude hypoxia severely affects the CNS and results in several physiological changes. The hippocampus is closely associated with learning and memory and an insult to this region affects cognition. Previous studies suggest that rapid or prolonged exposure to HBH is associated with psychomotor and cognitive impairments. The defense personnel, mountain climbers and rescue teams are exposed to such harsh environment and thus it demands a systematic study emphasizing the subtle effects of such extreme environments on cognitive function. To suggest a solution to this problem it is necessary to understand in detail the mechanisms of underlying cognitive deficits at HBH. We have demonstrated that the short-term hypobaric hypoxic exposure results in hippocampal dendritic atrophy and is associated with learning and memory impairment in adult rats. Further, chronic exposure to HBH severely impaired the learning and memory in radial arm maze task and this was associated with decreased hippocampal long-term potentiation (LTP) and reduction in the levels of biogenic amines and acetycholinesterase activity in the hippocampus. Our study suggests that hippocampal dendritic atrophy, reduced LTP, decreased cholinergic and aminergic neurotransmission on exposure to HBH could be the basis for the cognitive deficits. Understanding the neural basis of deleterious effects of HBH can lead to the development of therapeutic strategies in the treatment of high altitude associated disorders including cognitive decline.

Abs.S3.3

Differential Regulation of Autonomic Responses in Acclimatized Lowlanders on Prolonged Stay at High Altitude

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Global hypoxia at high altitude is reported to cause sympathetic dominance that may contribute to the pathogenesis of high altitude illnesses. Although, there is evidence that exposure to high altitude leads to several pathophysiological alterations including high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE), the effect of prolonged stay at high altitude on autonomic functions, however, remains to be explored. Thus, the present study aimed at investigating the duration dependent effect of high altitude on autonomic neural control of cardiovascular responses. A total of 229 subjects, 55 of the trans-Himalayan native population (4500 m),

58 of acclimatized low landers (ALL) staying at an altitude for < 6 months (4500-5000 m) and 60 of ALL staying for >18 months (4500-5000 m) were studied and compared with 56 of the sea level low landers (720 m). ECG recordings were measured and heart rate variability (HRV) parameters were calculated to determine the sympatho-vagal responses. The physiological indices viz. blood pressure, pulse rate, SpO2 and BMI were also investigated. Blood urea nitrogen, creatinine, serum lipids, alanine aminotransferase, aspartate aminotransferase, homocysteine, folate, Vitamin B12, Angiotensin II and angiotensin converting enzyme activity were also estimated from serum samples. We demonstrate here for the first time that prolonged stay at extreme altitudes >4500 m above sea level resulted in a persistent sympathetic dominance ($P<0.01$) when compared to sea level populations. The increased LF/HF ratio on 6 months stay ($P<0.01$) at high altitude was regulated by elevated Angiotensin II ($P<0.01$) while subsequent blunting of the vagal response on 18 months stay ($P<0.05$) could be attributed to increased homocysteine levels that were independent of folate concentration. Hence, our findings provide new insights to the sympathetic dominance at high altitude which is differentially regulated by angiotensin II and homocysteine depending on the duration of stay.

Abs.S3.4

Dyspnea at High Altitude

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Dyspnea is often defined as an abnormally uncomfortable awareness of breathing. Various terminologies such as, air does not go all the way down, tightness or tiredness in the chest, choking sensation, breathlessness, an urge to breathe etc., are often used by patients to describe dyspnea. Young subjects (soldiers) who are exposed to high altitude with established high altitude pulmonary edema (HAPE) complain of dry cough, breathlessness, and chest pain. Since HAPE is an end-stage where there is alveolar infiltration, it is likely that such symptoms are initiated much earlier when there is pulmonary congestion. Thus, there is the possibility that starting from the initial stage and proceeding to the later stage, the pulmonary sensory receptor afferent system may show a progressive stimulation.

This possibility was examined recently in rabbits. Adult rabbits (Group II, n=6) were exposed to an altitude of 15,000 feet for 12 hours in a high altitude simulation chamber. They were subsequently anesthetized and vagal afferent activity originating from airway rapidly adapting receptors (RARs) was recorded. Another group of rabbits (Group I, n=6) exposed to room air served as controls. Lung histology was performed in both the groups. It was observed that with this altitude, for this duration, when there was only pulmonary congestion, there was a significant increase in the basal activity of RARs in Group II compared to the basal RAR activity in Group I. When the duration of high altitude exposure was extended to 36 hours in another group of rabbits (Group III), there was alveolar edema. Again, there was an increase in the basal activity of RARs, which was significantly higher than those in Groups I and II. The results indicate that the RARs may

be an afferent mechanism for the respiratory symptoms reported by subjects who ascend to high altitudes with or without radiological evidence of alveolar infiltration.

Pulmonary hypertension is another prominent symptom of high altitude exposure. Even though hypoxia per se could raise the pulmonary artery pressure, it could also be due to increased production of vasoconstrictor neuropeptides such as substance P (SP). Evidence was obtained in Groups II and III that with the respective exposures, there was an increase in lung SP concentration. Additionally, in these two groups, even sub-threshold doses of SP stimulated the RARs significantly. The results indicate that at high altitude, endogenous SP may accentuate the respiratory symptoms through the stimulation of RARs.

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Symposium 4 (S4)

Abs.S4.1

A Role for mGluR5 in the Pathogenesis of Fragile X

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Fragile X (FX) is the leading inherited cause of mental retardation and an identified cause of autism. The metabotropic glutamate receptor (mGluR) theory of fragile X posits that FMRP and Gp1 mGluRs normally work in functional opposition, and that in the absence of FMRP, unchecked mGluR-dependent protein synthesis leads to the pathogenesis of FX. The goal of these studies was to test the mGluR theory. By reducing mGluR5 gene dosage by 50%, we were able to bring 7 of 8 fragile X phenotypes significantly closer to normal. Although the precise molecular basis of the interaction remains to be determined, the data show unambiguously that mGluR5 and FMRP act as an opponent pair in several functional contexts, and support the theory that many CNS symptoms in fragile X are accounted for by unbalanced activation of Gp1 mGluRs. These findings have major therapeutic implications for fragile X syndrome and autism.

Abs.S4.2

Calcium Channels and G Protein Coupled Receptors – a Lipid Connection

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Nociceptive stimulation from the periphery and visceral organs causes dorsal root ganglia neurons to release substance P (SP) onto the soma and dendrites of dorsal horn (DH) neurons. These DH neurons express tachykinin receptors (NK-1R) and N-type calcium channels (N-channels). SP, the principal neuropeptide mediating pain, binds to NK-1R. Pharmacological blockers of N-channels are used as analgesics thus implicating N-channels in pain perception. Yet the complete mechanism by which SP modulates N-channel activity is unknown. Gq-coupled M1 muscarinic receptors enhance and

inhibit native N-type calcium current (N-current) at negative and positive potentials respectively; arachidonic acid (AA) mimics this modulation. Blocking cytoplasmic phospholipase A2 (cPLA2) minimizes this modulation. Here, by monitoring recombinant channel (Cav2.2, α2δ and β3) activity in HEK-293 cells using whole-cell patch clamp techniques, we show that N-current inhibition by 250 nM SP involves NK-1R activation of extracellular receptor kinases (ERK1/2), PLA2 and downstream release of fatty acids, possibly AA. In separate studies, ERK1/2 activation has been reported downstream of Gq-coupled NK-1R activation and upstream of cPLA2 activation. Here we show that activation of NK-1R, ERK1/2 and PLA2 occur in a linear pathway leading to N-current modulation. We also show that SP inhibits or enhances N-current depending on the type of β subunit co-expressed with N-channels. While β3-containing channels exhibit inhibition, β2a-containing channels exhibit enhancement. Among the different β subunits, β2a is uniquely palmitoylated on its two amino-(N-) terminal cysteine residues. We previously hypothesized that the palmitoyl groups on β2a block N-current inhibition to reveal latent enhancement. Using HEK cells expressing NK-1R, Cav2.2, β3, α2δ and eGFP, we found that pre-incubation of cells with free palmitic acid (10 μM) eliminates SP-mediated inhibition of N-current that normally occurs with β3 expression. In contrast, direct application of palmitic acid has no effect of its own on N-channel activity. These findings support our model that palmitoylation is necessary and sufficient to block inhibition of N-current. This novel role of palmitoylation provides a possibility of plasticity at a molecular level in the pain pathway

Abs.S4.3

Disruption of Calcium Signaling in Neurons in Cerebral Ischemia : Role of AMPA Receptors

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The pathogenesis of cerebral ischemia involves massive ATP depletion leading to loss of ion homeostasis in neurons. Ample evidence shows that intracellular calcium ([Ca2+]i) overload as a consequence of cerebral ischemia is a major contributing factor towards acute and delayed neuronal injury. Multitudes of mechanisms have been suggested to elevate neuronal cytosolic calcium. Amongst these the [Ca2+]i rise mediated by elevated extracellular glutamate is proposed to be a key regulator of neuronal injury. Both NMDA and AMPA subtype of glutamate receptors have been implicated in mediation of glutamate induced [Ca2+]i rise. NMDA mediated [Ca2+]i increase and subsequent neuronal injury has been extensively studied. Some of the recent studies indicate a more central role for AMPARs as their antagonists are potentially more effective in neuroprotection that NMDA antagonists in rat models of cerebral ischemia. AMPARs undergo constitutive and synaptic activity dependent translocation from intracellular pools to membrane surface. Activity of AMPA receptor-channels, which are heterotetramers of GluR1-4 subunits, depends on its subunit composition. The functional AMPARs which are assembled from GluR1, 3, 4 subunits are permeable to calcium whereas GluR2 containing AMPARs are impermeable to divalent cations. Few recent reports have suggested that following

ischemia GluR2 subunit surface expression is reduced and GluR2 lacking AMPARs are directed to synaptic sites resulting in delayed neuronal injury.

Based on this evidence we investigated the involvement of AMPARs in mediating acute and delayed Ca2+ rise and resultant toxicity in rat hippocampal neuronal cultures using oxygen glucose deprivation as an in vitro model for ischemia. Quantitative measurements by fluorescence imaging suggest equal contribution of both AMPA and NMDA receptors in inducing [Ca2+]i rise during the acute phase of ischemia. Interestingly, contrary to earlier reports our study shows no enhancement in AMPA induced [Ca2+]i rise in post ischemic hippocampal neurons. This suggests that electrophysiologically measured increase in GluR2 lacking AMPAR current is not translated into significant AMPA receptor mediated cytosolic elevation in calcium.

Abs.S4.4

HIV-1 and Drugs of Abuse – *It Takes Two to Tango*

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Central nervous system (CNS) infection by HIV-1 cause glial cell mediated irreversible damage to the neurons leading to progressive motor and cognitive dysfunctions and other dementia like symptoms, collectively called HIV-associated neurocognitive disorders (HAND). Our findings suggest HIV-1 transactivating protein, Tat affects proliferation and differentiation ability of human neural stem cells. An enhanced damage to brain functions has been reported in HIV/AIDS patients that are drug abusers. Several experimental studies in primates and human postmortem studies have revealed that damage to dendritic spines, synaptic functions, neurons and glial cells is far greater than in cases not exposed to drugs of abuse. However, the molecular mechanisms underlying opioid mediated enhancement of HIV neuropathogenesis are still unknown and warrant extensive explorations. We attempted to fill this gap by a step wise approach using a well characterized human neuronal cell culture system. We studied neuronal damage by looking into alterations in mitochondrial functions and cell signaling mechanisms of neurons exposed to the double insult of HIV-1 Tat and Morphine. Significant alterations in mitochondrial membrane homeostasis were observed following co-exposure of neuronal cells to HIV Tat and morphine. Extensive studies into MAPK signaling pathways revealed involvement of JNK and ERK1/2 pathways in enhanced toxicity of Tat and morphine. Our findings provide insights into cellular and molecular basis for the enhanced damaged seen in neuronal cells due to co-morbidity of HIV-1 viral proteins and morphine. These findings correlate well with clinical observation of enhanced cognitive and motor deficits in drug abusing HIV/AIDS patients.

Abs.S4.5

Plasticity of Inhibition in the Basolateral Amygdala

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The lateral amygdala (LA) plays a key role in emotional learning and is the main site for sensory input into the amygdala. Within the LA, pyramidal neurons comprise the major cell population with plasticity of inputs to these neurons thought to underlie fear learning. Pyramidal neuron activity is tightly controlled by local interneurons, and GABAergic modulation strongly influences amygdala-dependent learning. Synaptic inputs to some interneurons in the LA can also undergo synaptic plasticity, but the identity of these cells and the mechanisms that underlie this plasticity are not known. We show that long-term potentiation (LTP) in LA interneurons is restricted to a specific type of interneuron that is defined by the lack of expression of synaptic NR2B subunits. We find that LTP is only present at cortical inputs to these cells and is initiated by calcium influx via calcium-permeable AMPA receptors. LTP is maintained by trafficking of GluR2-lacking AMPA receptors that require an interaction with SAP97 and the actin cytoskeleton. Our results define a novel population of interneurons in the LA that control principal neuron excitability by feed-forward inhibition of cortical origin. This selective enhanced inhibition may contribute to reducing the activity of principal neurons engaged during extinction of conditioned fear.

Symposium 5 (S5)

Abs.S5.1

Introduction to Biologics

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Biologics include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized. Better understanding of pathogenic processes, particularly the immune system, topped with advances in medicinal chemistry has led to the evolution of biologics as therapeutic agents. In the previous decade several biologics were approved for human use to address the unmet medical needs of conditions such as cancer, rheumatoid arthritis, psoriasis, ulcerative colitis, etc.

The bench to bedside process of biologics development albeit similar to the drug development process has certain peculiarities. These may include identification of appropriate animal species for toxicity testing, dosage conversions, development of analytical methods and a possibility of life threatening unpredictable adverse effects (TGN 1412). Cost of biologics (running into lakhs of rupees), resurgence of latent tuberculosis are the other issues pertinent to developing countries like ours. Unlike the generics available for off-patent drugs, the processes and regulatory issues for biosimilars need to be streamlined. To top it the real efficacy of many of these agents is only in a small subset

of population. These and other emerging facts are important for health care policy makers particularly in resource limited settings like ours.

Considering the fact that biologics are currently nearly 30 billion dollar market and the fact that drug pipeline is constantly diminishing, pharmaceutical companies are increasingly shifting their focus to biologics. However, since most of the lead research that leads to the development of biologics, takes place in academic institutes, these figures may be disproportionately inflated for the interest of innovator companies. Pharmaceutical companies and regulatory agencies are gearing up to tap this market. For the interest of health sciences, academic research institutes should take the lead in pioneering research to unmet medical needs and partner with government and pharmaceutical companies to develop cost-effective biologics for greater common good.

Abs.S5.2

Special Aspects of Conducting Clinical Trials with Biologics

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Broadly, biologics include proteins, antibodies, peptides, and some vaccines. Most of the times their route of administration is parenteral as they are poorly absorbed orally.

Clinical trials are needed for new drugs including biologics to demonstrate that the product is safe and effective. These trials are planned and conducted by the sponsor, which is usually a biotech company in case of biologics.

These trials need to be conducted as per GCP, international and national regulatory guidances as well as ethical principles. Most of the aspects of conducting these trials remain similar in case of drugs and biologics although there a few differences.

The fundamental issues related to clinical trials remain unchanged, i.e. a controlled trial, control can be concurrent (placebo, active drug) or historical; randomization, if applicable; blinding, if possible; and so on. It is the responsibility of the Investigators to choose the most appropriate design that will help them answer the scientific question posed by the trial. The other elements like inclusion/ exclusion criteria, methods of measurement, adherence, etc are all broadly similar.

Early exploratory trials with biologics do present some challenges distinct from those seen with “typical” drugs. For instance, about 25% of patients with inflammatory bowel disease that participated in the early clinical trials of the biologic agent infliximab developed severe delayed hypersensitivity reactions due to development of anti-infliximab antibodies after they were re-exposed to inflixamab after its marketing, preventing them from using that drug even though they had responded well in the trials.

Also, in phase 1 trials, the risk benefit assessment with biologics is different as compared to drugs and in many of the phase 1 trials, patients are recruited instead of healthy volunteers. Moreover, the instead of the concept of maximum tolerated dose we may use “less is more”. The FDA guidance on safe starting dose for biologics should be

seen when planning phase 1 trials. It may be preferable to estimate the starting dose using the Minimal Anticipated Biological Effect Level (MABEL) in addition to NOAEL. Staggered enrolment is preferred so that there is sufficient time between two dose levels. The methods of evaluation of safety of the new agent are also different as biologics present greater challenges – keep in mind particularly the Tegenero experience. Dose escalation schemes may involve lesser increments as compared to drugs and Bayesian methods are useful.

Adaptive designs may be preferable in phase 2/3 trials with biologics to maintain a greater degree of flexibility in the trial design so that incoming information is taken into consideration while proceeding further. Safety considerations are of prime importance because the biologic agents have the potential to lead to derangement in multiple cascading pathways in the organism. Manufacturing issues also assume greater importance because impurities can severely jeopardize the safety of the compound. Risk of infections may be greater with biologics and longer follow-up periods may be needed to detect some adverse effects because of their nature.

Abs.S5.3

Development of Biosimilars : Challenges and Opportunities

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Biosimilars are products similar in quality, safety and efficacy to the originator's licensed biological products. Due to high cost of therapy, biological products have remained out of reach of majority of the people in developing countries. Thus a huge need exists for biosimilars in countries like India. As per the market research, biological products with global sales of over $60billion will lose patent protection over the next 5 years. Indian Pharmaceutical industry, having already developed and launched biosimilars, is poised to play a major role in the global biosimilars' market.

The pharmaceutical industry has evolved from developing non-specific natural products to developing highly specific chemical drugs and biological drugs. Developing generic versions for chemical drugs is relatively easy due to precise chemical processes involved and the small size of the molecules. However, complexities of structure and massive size of the protein molecules, and the complex manufacturing and production processes makes development of biological products which are absolutely identical difficult. As the manufacturing process for a biosimilar is different from that of the innovator's product, some differences in the final product are expected. However, even minor changes in manufacturing process can affect the three dimensional structure of the protein, the post-translational modifications such as glycosylation profile and the impurity profile of the product. These subtle differences can alter the quality, efficacy and safety of the product, including immunogenicity. Thus the CMC, non-clinical and clinical studies of biosimilar products need to be more extensive than the pharmaceutical and bioequivalence studies for generics of chemical drugs.

Guidance documents regarding data to be generated for licensing of biosimilar drugs are

available from the EMEA, WHO and various regulatory agencies including Korea and Malaysia. All guidance documents stress on exhaustive comparative studies of the biosimilar product with the reference biological product, including physicochemical and in-vitro biological similarity, comparative non-clinical pharmacodynamics and toxicology, and therapeutic equivalence. In addition, extensive immunogenicity studies need to be conducted in human subjects as the animal studies are usually not predictive of the immunogenicity in humans. Further, the immune reaction to impurities can render the developed product non-similar to the reference product. Due to complexities involved, a case-to-case approach is thus needed for the development of biosimilar products.

In addition to complexities involved in the development of biosimilars, examples of successful and unsuccessful attempts at developing biosimilars will also be discussed during the talk.

Conclusion: Development of biosimilars is complex and challenging. Companies that are able to overcome these hurdles will likely play a major role in the pharma sector in the future.

Symposium 6 (S6)

Abs.S6.1

Diabetic Cardiomyopathy : Insights into Pathogenesis and Therapeutic Approaches

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Cardiovascular disease is responsible for 80% of deaths among diabetic patients much of which has been attributed to coronary artery disease. There is an increasing recognition that diabetic patients suffer from an additional cardiac insult termed “Diabetic cardiomyopathy”. Experimental as well as clinical studies suggest that extensive metabolic and molecular changes may underlie both functional and structural alterations of the diabetic myocardium.

Translational studies are, however, limited and only partly explain why diabetic patients are at increased risk of cardiomyopathy and heart failure. The most important mechanisms of diabetic cardiomyopathy are metabolic disturbances (alteration of glucose transporters, increased free fatty acids, carnitine deficiency, changes in calcium homeostasis), myocardial fibrosis, cardiac autonomic neuropathy (denervation and alterations in myocardial catecholamine levels), epigenetic changes and insulin resistance. Treatment paradigms are very much limited to interpretation and need more attention. There is an urgent need to conduct pathogenetic, diagnostic and therapeutic studies specifically in diabetic patients with cardiomyopathy to better understand the molecular mechanisms which initiate and progress diabetic cardiomyopathy and to formulate more effective and appropriate treatments.

Abs.S6.2

The Space Odyssey of Heart : Pharmacological Protection for the Heart in Space

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During spaceflight, astronauts experience microgravity which has profound effects on the circulatory system. Though the heart and the vascular system is adapted to work against gravity, a new environment such as microgravity makes adaptation difficult since the heart no longer has to work hard, partly because there is less fluid to pump through and so it shrinks. Nitric Oxide (NO), a vasodilator and signaling molecule, is an important determinant of basal cardiac functions. Alteration of NO metabolism is primarily responsible for the associated cardiovascular deconditioning. Our previous work showed that microgravity induces NO production in endothelium and promotes angiogenesis. Based on those observations, we hypothesize that altered gravity disturbs NO homeostasis in the heart as well to bring about cardiac malfunctions.

To study cardiac functions in-vivo under altered gravity, we subjected zebrafish and chick embryos to alerted gravity by employing the in-house fabricated clinostat, which simulates microgravity. The heart rate of zebrafish and chick was calculated from videos records of heart movements after two hours of treatment with gravity or microgravity in the presence and absence of NO. We observed that microgravity increases the heart rate in zebrafish. Simultaneously we also monitored NO production in the heart under microgravity treatments. The heart rate of the chick and zebrafish embryos came back to normal when they were treated with specific NO scavengers. Further, we studied the mechanistic aspects of microgravity perturbations in cardiac functions in relation to NO. The results of the study indicate that microgravity promoted NO modulates actin polymerization of cardiomyocytes to enhance the heart beat under altered gravity conditions.

We conclude that NO recovers altered gravity effects on cardiovascular system in chick and zebrafish respectively.

This work was supported by a grant from Indian Space Research Organization (ISRO) (Microgravity: Anna-Univ:11) to SC.

Abs.S6.3

Regeneration of Infarcted Myocardium with Resveratrol-modified Cardiac Stem Cells: Role of Micro-RNA

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The major problem in stem cell therapy includes viability and engraftment efficacy of the stem cell after transplant. Indeed, the vast majority of host-transfused cells do not survive beyond 24 to 72 hours. In order to increase survival and engraftment of implanted cardiac stem cells in host we developed a technique of treatment of the cells with resveratrol, and tested this technique in rat model of LAD (the left anterior descending) occlusion. With this goal the multipotent clonogenic cardiac stem cells (the cardiac stem cells) isolated from rat heart were stably transfected with EGFP for purpose of tracking in tissue and were

pre-treated with 2.5 µM resveratrol for 60 minutes. Rats were anesthetized, hearts opened and the LAD was occluded to induce heart attack. The animals were divided into two groups each of them was subjected to transplant with either resveratrol-treated or resveratrol-non-treated cardiac stem cells. One week after the LAD occlusion, the cardiac reduced environment was confirmed in resveratrol treated rat hearts by the enhanced expression of nuclear factor-E2-related factor-2 (Nrf2) and redox effector factor-1 (Ref-1). M-mode echocardiography was performed to determine cardiac function up to four months after the stem cell therapy. Initially after 7 days, both groups revealed improvement in cardiac function, but only resveratrol-modified stem cell group revealed improvement in cardiac function (left ventricular ejection fraction, fractional shortening and cardiac output) at the end of one month, two months and four months period. The improvement of cardiac function was accompanied by the enhanced stem cell survival and proliferation as evidenced by the expression of cell proliferation marker Ki67 and differentiation of stem cells towards the regeneration of the myocardium as evidenced by the expression of EGFP up to four months after LAD occlusion in the resveratrol treated stem cell group of hearts. Some of the results were substantiated with the results of microRNAs. Our results demonstrate that resveratrol maintained a reduced tissue environment by over-expressing Nrf2 and Ref-1 in rat heart up to four months resulting in an enhancement of the regeneration of the adult cardiac stem cells as evidenced by increased cell survival and differentiation leading to improved cardiac function. Expression of SDF and myosin conclusively demonstrated homing of stem cells in the infracted myocardium, its regeneration leading to improvement of cardiac function. Role of microRNAs will also be discussed.

Abs.S6.4

Molecular Mechanisms in Endothelial Regulation of Cardiac Function

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Endothelium is now recognized as a massive, regionally specific, multifunctional organ. Given its strategic anatomic location between the circulating blood components and the vascular smooth muscle or the cardiac muscle, it is a biologically significant interface whose dysfunction can be a critical factor in various pathological conditions. Two types of endothelial cells are recognized in the heart, the endocardial endothelial (EE) cells and the microvascular endothelial cells (MVE). Both produce common autacoids and share similar roles in signal transduction induced by neurotransmitters, hormones or mechanical stimuli. They are however two distinct cell populations with dissimilar embryological origin, cytoskeletal organization, receptor mediated functions and electrophysiological properties. Both the MVE and EE are modulators of cardiac performance. Myocardial contraction may be modulated by cardioactive agents such as nitric oxide, prostanoids, endothelin, natriuretic peptides, angiotensin II, kinins, reactive oxygen species and adenyl purines released from the cardiac endothelium. Two mechanisms have been proposed for the signal transduction from EE to the underlying

myocytes: stimulus-secretion-contraction coupling and blood-heart barrier. Nitric oxide, bradykinin and myofilament desensitizing agent are probably important in short-term regulation of myocardial functions. Endothelin and Angiotensin II are probably involved in long-term regulation. Besides its sensory function and paracrine modulation of myocardial performance, EE as a blood-heart barrier could be of significance for the ionic homeostasis of the cardiac interstitium. In cardiac diseases, the damage to EE or MVE leading to failure of the endothelial cells to perform its regulatory and modulator functions may have serious consequences. The influence of EECs on cardiac fibroblasts is of considerable interest because cardiac fibroblasts, as the principal cellular constituent of the interstitium, play an important role in maintaining the structural and functional integrity of the myocardium. Specifically, the effects of paracrine factors, such as ET-1 and TGF-â derived from EECs, on cardiac fibroblast proliferation and collagen synthesis are of interest. Our studies have demonstrated the influence of endocardial endothelium on cardiac interstitium that could contribute to the development of myocardial fibrosis and ventricular remodeling. A better understanding of the endothelial signaling pathways in cardiac physiology and pathophysiology may lead to the development of novel strategies for therapy in cardiac failure.

Abs.S6.5

Functional Variants of the Physiological Anti-hypertensive Peptide Catestatin in an Indian Population

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Catestatin, an endogenous cationic and amphiphilic peptide, is a novel regulator of blood pressure and cardiac functions. It is generated by proteolytic cleavage of the prohormone chromogranin A, a major protein co-stored and co-released with catecholamines from the storage vesicles in adrenal chromaffin cells and adrenergic neurons. Catestatin potently inhibits catecholamine release by acting on the neuronal nicotinic acetylcholine receptor (nAChR) as a non-competitive antagonist. Recently, we have sequenced the catestatin region in an Indian population (~500 hypertensives and ~500 normotensives) and discovered two variants of this peptide: Gly364Ser and Gly367Val. As many as ~15% of our population harbors these variants. Interestingly, while the 364Ser variant is about 3-times more frequent in our study population as compared to a European population, 367Val variant is a novel one in our Indian population. Subjects with 364Gly/Ser genotype display lower systolic blood pressure than those with 364Gly/Gly genotype. This is consistent with the significantly lower levels of plasma catecholamines in subjects having the 364Gly/Ser genotype. Functional analyses in chromaffin cells using synthetic peptides show that both these catestatin variants are significantly less potent than the wild-type peptide. Structural analysis reveals that the differential potencies of the catestatin variants arise due to alteration in the secondary structure of the peptide leading to altered interaction with the nAChR (viz. binding affinity with the receptor as well as the extent of blockade of the receptor pore). These findings provide new insights into the mechanism of blood pressure regulation.

Abs.S6.6

Differential Adrenergic Signaling in Heart : When and How It Goes Wrong

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Depending on the dose, norepineprine (NE) can induce hypertrophy or apoptosis in cardiac myocytes. Reactive oxygen species (ROS) play a key role in mediating both responses, but the mechanisms are not understood as yet. Nonetheless, the two pathways are marked by the differential induction of fosB and fra-1, two genes encoding closely related members of the AP-1 family of transcription factors. Although NE induces both the genes via reactive oxygen species (ROS), the two pathways are mechanistically different and depend upon the cellular context. Molecular analysis suggests that multiple cis-elements in the gene promoters mediate the redox response wherein transcription factor SP-1 is a direct sensor of cellular redox state. To further delineate the biochemical basis of such differential redox signaling; we observed that H9c2 cardiac myoblasts upon treatment with 2 ìM NE (hypertrophic dose) generate ROS only till 2 hours, while those treated with 100 ìM NE (apoptotic dose) sustains it till 48 hour, till the onset of apoptosis. Noticeably, although the levels of ROS were comparable under both the treatments, it was differentially quenched by various ROS quenchers, suggesting the existence of NE dose specific assortment of ROS. NE treatment (2 and 100 ìM) also caused sustained generation of HPF sensitive highly reactive species peroxynitrite. However, oxidative DNA damage, as measured by the increase in 8-OHdG content; and induction of GRP78, a hallmark of ER stress/unfolded protein response; was seen only in cells treated with the 100 ìM dose of NE. This study thus infers that hypertrophic and apoptotic doses of NE generate distinct RO/NS profile leading to discrete downstream effects.

Abs.S6.7

Novel Pharmacological Strategies for Cardiac Hypertrophy

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Soy intake has been associated with low prevalence of chronic diseases, like cancer and cardiovascular diseases. This has been especially observed in Asian population where soy is widely consumed as soy milk, soy flour, isolated soy protein and soy concentrates. Soy is rich in isoflavone content especially, genistein which possesses phytoestrogenic and antioxidant properties. Experimental studies have shown that genistein prevents right ventricular hypertrophy and vascular remodeling. However, no information is available on its effect on left ventricular hypertrophy, an important risk factor for heart failure and sudden cardiac death. Therefore, we have evaluated its preventive potential in isoproterenol-induced left ventricular hypertrophy in rats. The study was approved by the Institute Animal Ethics Committee in compliance with the NIH guidelines.

Laboratory bred male Wistar rats (150-200 gm, 10-12 weeks old) were randomly assigned to different experimental groups. Isoproterenol (5 mg/kg, body weight) was injected subcutaneously once daily for 14 days to induce cardiac hypertrophy. Two doses of genistein (Sigma, India; 0.1 and 0.5 mg/kg, s.c. once daily), were administered along with isoproterenol. In separate groups, L-NAME (2 mg/kg; non-selective NOS inhibitor) and aminoguanidine (100 mg/kg; selective iNOS inhibitor) were administered either alone or along with isoproterenol and/or genistein. Rats were subjected to two dimensional M-mode echocardiography for the estimation of LV mass and % fractional shortening (% FS). Heart samples were analyzed for TBARS, GSH, SOD and catalase levels. Formalin stored hearts were used for histopathology, myocyte size and picro sirius red stain for fibrosis. Isoproterenol treatment caused significant increase in heart weight to body weight ratio ($P<0.001$). Genistein (0.1 and 0.2 mg/kg) significantly prevented these effects ($P<0.001$). However, L-NAME prevented this salutary effect of genistein, while aminoguanidine did not. Similarly L-NAME only prevented the salutary effects of genistein on isoproterenol-induced increase in IVS thickness ($P<0.001$), posterior wall thickness ($P<0.05$) and myocardial collagen content ($P<0.001$). Genistein prevented isoproterenol-induced increase in myocardial oxidative stress as manifested by increase in TBARS, accompanied with decreased levels of SOD, catalase and GSH. While L-NAME prevented this beneficial effect of genistein, aminoguanidine did not have any modulatory effects. Genistein significantly prevented isoproterenol-induced increase in myocyte size ($P<0.001$). Only L-NAME, but not aminoguanidine prevented this effect. Similarly L-NAME prevented the salutary effect of genistein on isoproterenol-induced increase in fibrosis ($P<0.001$).

NO plays an important role in cardiac hypertrophy and remodeling. Transient and low release of NO by eNOS has been shown to be beneficial, while high and sustained release by iNOS may be detrimental. In our study, the beneficial effects of genistein on isoproterenol-induced cardiac hypertrophy was blocked by a non-selective iNOS inhibitor and not by a selective iNOS inhibitor. Interestingly, the selective iNOS inhibitor per se prevented isoproterenol-induced cardiac hypertrophy. This highlights that genistein acts through inhibiting iNOS and increasing eNOS activity, the latter effect when blocked by L-NAME caused a loss of the beneficial effect of genistein.

Symposium 7 (S7)

Abs.S7.1

Psycho-Physiology of Meditation

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Meditation is not an irrational emotional or religious experiences but a deliberate mental operation of psychoanalysis. It is a form of psychotherapy for destroying the repressing and repressed forces which have produced and would continue to produce inhuman tendencies and irrational behavior if not destroyed. Eradication of these forces

would enable us to develop our true human nature and justify our claim of being the highest product of the cosmic process. A secondary benefit of meditation is generally known as 'relaxation', which accurse incidentally from its practice. Relaxation is the result of triggering of an innate protective mechanism, which counteracts the dangerous effects of environmental and emotional stresses. Physiological functions could be controlled through various meditational techniques. Regular practice of meditation could reduce the blood-pressure, heart-rate and metabolism. Modern scientific investigations have confirmed that (i) meditation produces change in the bioelectrical activity in the nervous system; (ii) omission of more Alpha brain waves representing the state of calmness; and (iii) mechanism of the autonomous nervous system can be activated through the control of certain voluntary mental actions. Scientific investigations have also provided evidence that meditation can influence the control or command mechanisms which are ultimately responsible for the homeostasis in the body. In addition to that meditation is also an apparatus for regulating and controlling one's bestial instincts of anger, aggression, cruelty, vindictiveness and fear; it is a tool for awakening and developing one's conscious reason and thereby modifying one's thoughts, actions and behaviour to be truly worthy of a human being; it is a process of remedying inner incompleteness and reducing inner discord. It may be proactive to acquire not only psychical goodness but also to acquire psychical goodness too by eradicating all evil from one's thoughts, speech and action. An objector may at this point raise a doubt that anger, fear, aggression, etc., are natural components of human nature which cannot possibly be changed. To this, a reassuring answer comes from modern psychology and endocrinology. Mental states, emotions and behavioural pattern of an individual are profoundly influenced by the synthesization of hormones secreted and distributed by the ductless glands. In fact all passions, emotions and impulses are the expressions of the endocrine system. And so, when we talk of human nature, we really mean its expression and this can most definitely and thoroughly be changed by controlled mental practices. Since mental tendencies and human behavior are almost completely governed by the integration of neuro-endocrine products, transmutation of the latter must produce the desired development of the integrated personality of man. Removal of all psychological distortions-hate, fear, cruelty, etc. through transmutation of chemical messengers will immensely strengthen the endocrine secretions are modified and controlled by conscious reason, the repressed and repressive forces building up the psychological explosive will be defused and lose its power to overwhelm and distort the rational judgment. This can be achieved through meditation only. The pathway of mechanism explaining the stepwise details of the operations will be discussed.

Abs.S7.2

Yoga as an Intervention for Mental Health

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The pace and demands of modern society are subjecting many individuals to the burden

of continuing and often chronic stress at both work and home. Unmanaged stress is now believed to be one of the most consistent predictive factors contributing to the development of mental health and behavioural problems in both adolescents and adults. Statistics suggest that the majority of adolescents and adults will experience a mental health disorder in their lifetime. Although personal resources such as mastery and self-regulation skills are known to be consistently associated with enhanced resilience to the onset of mental health disorder episodes, our society has no established training or education programs in our schools or workplaces for stress management. Yoga is a comprehensive and holistic set of mind-body practices including physical exercises and postures, breathing techniques, relaxation strategies, meditation/ mindfulness practices and applied psychology/ philosophy. Research studies have shown that yoga is highly effective in the management of acute and chronic stress both psychologically and physiologically. Furthermore, a growing body of clinical research trials has indicated that a variety of mental health conditions can be effectively managed with therapeutic application of yoga practices. This presentation will overview the evidence for the preventive and therapeutic application of yoga for mental health and the potential underlying mechanisms of its action.

Abs.S7.3

Effect of Yoga and Lifestyle Interventions on Risk Factors of Metabolic Syndrome

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Excess of body fat is associated with severe risk factors and may develop Metabolic Syndrome X (MS) which is characterized by central obesity, hypertension, impaired glucose tolerance, low HDL Cholesterol levels, and/or hypertriglyceridemia. Abdominal obesity is associated with an excess accumulation of visceral fat which is an important correlate of the insulin dyslipedemic syndrome.Role of yogic exercise in preventing the progression of metabolic syndrome has been recognized. Lifestyle interventions have clearly shown that a well-designed exercise programme produces several beneficial effects in well-motivated obese subjects. Effect of a yoga practice for 12 weeks on lipid profiles of 56 obese subjects (32 females and 24 males) age ranged from 20 to 45 yrs were evaluated. Results revealed a significant ($P<0.01$) decrease in anthropometric variables (weight, body mass index, waist circumference and hip circumference). Further, total cholesterol, triglyceride, very low density lipoprotein, low density lipoprotein and fasting plasma glucose decreased significantly ($P<0.01$) while high density lipoprotein increased significantly when compare to the basal variables before intervention given ($P<0.01$). A significant and positive correlation was evident among pretreatment anthropometric variables ($P<0.01$) while most of the lipid profiles parameters also showed a significant ($P<0.05$ or $P<0.01$) positive or negative correlation with each other. The pretreatment weight ($r=0.49$; $P<0.01$), waist circumference ($r=0.39$; $P<0.01$) and hip circumference ($r=0.26$; $P<0.05$) showed significant and positive correlation with pretreatment triglyceride. The change (improvement) in weight and TG were significantly ($r=0.49$, $P<0.01$) associated with each other. Thus, yoga may be an adjuvant

therapy for the management of risk factors for metabolic syndrome.

Abs.S7.4

Importance of Yoga and Naturopathy based Healthy Life Style and Diet Practices

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The prevalence of chronic diseases such as Hypertension, Diabetes Mellitus, Coronary Artery Disease, Back Pain, Asthma, Arthritis etc are rapidly increasing in developing countries. Epidemiological studies in India have revealed that the prevalence of these chronic diseases are increasing with the time. If current trends continue they anticipate that number to essentially double. This increase, most marked in the urban population, is likely to be related to changing life-styles and stress. The increased economy has brought us all the comforts has led to reduced physical activity and recourse to wrong way of habits and dietary patterns such as consuming excess tea, coffee, developing a habit of smoking, drinking alcohol, consuming high spicy and processed foods etc have led to the occurrence of these life style chronic disorders. Studies have clearly shown that all these chronic conditions are related to each other, presence of one condition predisposes to occurrence of other condition. Promising in this regard is appropriate healthy living habits such as physical activity, regulated dietary habits, proper relaxation, good sleep and stress free life. Studies have clearly shown to reduce body weight, BP, glucose level and cholesterol. Yoga & Naturopathy as a way of life forms a healthy life style system consisting of various postures (Asana), breathing (Pranayama), Relaxation techniques and meditation techniques and ancient healthy practices such as massage, fasting, hydrotherapy etc have been shown to have therapeutic benefits for individuals with a wide range of health conditions, including hypertension, diabetes, asthma, arthritis, back pain etc. Yoga also is effective in reducing stress and improving exercise tolerance as it is related to cardiovascular response.

Symposium 9 (S9)

Abs.S9.1

Patho-physiology of Oxidative Stress in Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is characterized by repetitive cycles of hypoxia and reoxygenation that promotes the formation of reactive oxygen species (ROS) and nitrogen species (RNS). Reactive oxygen and nitrogen species are molecules with unpaired electron(s) in their outer orbit. These electrons render them highly prone to chemical reactions. ROS such as superoxide anion (O2–), hydroxyl radical (OH–) and peroxynitrite (ONOO–) are injurious to cells through a process called lipid peroxidation, which damages cell membranes and generates more ROS and RNS in a chain reaction.

The imbalance between oxidant producing systems and antioxidant defense system reduces the bioavailability of nitrous oxide. This contributes to oxidative/nitrosative stress in the vasculature that affects endothelial function, vascular inflammation and atherosclerosis. In health, homeostasis is provided by the redox balance system. Oxidative stress activates redox-sensitive transcription factors which regulate inflammatory cytokines, chemokines and adhesion molecules.

Intermittent hypoxia results in activation of pro-inflammatory transcription factors such as nuclear factor kappa B (NF-kB) and activator protein (AP)-1. These promote activation of various inflammatory cells, particularly lymphocytes and monocytes with the resultant expression of pro-inflammatory mediators that may lead to endothelial dysfunction. TNF-alpha and IL-6 in particular could play a major role.

Two major mechanisms have been proposed to explain the morbid consequences of OSA, namely increased generation and propagation of reactive oxygen species and initiation and amplification of inflammatory processes. OAS exerts an enhanced intravascular oxidative stress reaction. Oxidative stress is linked to CVD with increased adhesion to endothelial cells.

Abs. S9.2

Sleep Deprivation : Are the Effects Different in a Developing Brain ?

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Study Objectives : To examine the effects of acute and chronic sleep deprivation (SD) on spatial learning, reference memory and hippocampal longterm potentiation (LTP) in pubertal mice.

Design and Measurements : Pubertal C57/Bl6 strain of mice, were subjected to acute SD for 72 hrs or chronic SD for 2 weeks starting at P24. Chronic group were further subdivided into chronic sleep restriction (chronic-SD) or chronic sleep fragmentation (SF). Spatial learning and memory was examined using Morris water maze studies, and LTP was examined after stimulation of schaffer collaterals in CA-1 region of hippocampus in all groups at the end of SD protocol. Animal actigraphy was used during the period of SD to monitor rest-activity patterns.

Results : A significant impairment of spatial learning and reference memory as well as LTP induction and maintenance in pubertal mice is seen with 72 hrs of acute-SD, but not with chronic sleep restriction or fragmentation. Actigraphy showed no “shifts” in the circadian rest-activity patterns during the period of SD in any of the groups compared to controls while activity counts are higher during periods of SD. Stress was not a factor in the SD methodology used.

Conclusions : During development acute SD is associated with impaired learning and memory as well as synaptic plasticity. Similar impairment was not seen with chronic sleep restriction or fragmentation in pubertal mice perhaps due to adaptation or compensation by allosteric or homeostatic responses. Further studies are needed to understand the molecular mechanisms of differences seen with acute and chronic sleep loss.

Abs. S9.3

REM – Sleep Disorders

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REM sleep is characterised by atonia of voluntary muscles except extraocular muscles, elevated autonomic activity and dreaming. REM related parasomnias might involve either the incoordination of these processes or the inappropriate admixture of REM sleep and wakefulness.

REM Behaviour Disorders (RBD), sleep paralysis and nightmare disorders are REM sleep related sleep disorders. RBD are characteristically acute/chronic forms where acute form is associated with drugs or even withdrawal of alcohol. Chronic form can be idiopathic or secondary to neurological diseases eg. Parkinson's disease. Polysomnography (PSG) is necessary for confirming the diagnosis. The sleep study shows that amount and cycling of sleep stages from NREM to REM is normal. Elevated muscle tone or increased phasic muscle activity in submental or anterior tibialis EMG during REM sleep is seen. Sometimes gross/subtle body movements may be recorded. PSG may be helpful in excluding other causes of sleep problems leading to RBD like Sleep disordered breathing.

Sleep paralysis refers to a conscious state at the onset or offset of sleep associated with paralysis of voluntary musculature,probably due to inappropriate REM intrusion into wakefulness or the failure to mantain sleep during REM persists. Typically occur in first two hours of sleep or at the time of final awakening.

Nightmares occur in the latter third of the night when REM proportion is increasing. Nightmares are not associated with overt motor dream enactment but are characterised by recurrent dreams followed by awakening with often detailed recall of the dream and fear is the most predominant emotion recalled.

REM sleep disorders should be distinguished from other forms of parasomnias and also from other sleep disorders which may aggravate or coexist with these disorders should also be ruled out.

Abs.S9.4

EEG Dynamics after Acute and Chronic Sleep Loss

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Examination of the global features of EEG is traditionally practiced to derive the underlying neurophysiological connotations during different vigilant states. The EEG signals are generated regionally in neuronal populations of various cortical modules and their emergent interactions contribute to global patterns in the EEG. It is interesting to monitor the micro-features of EEG at the level of single neuron in individual cortical units and at the subcortical levels. The rest-activity in form of sleep-wakefulness is a dynamic EEG construct of underlying neural networks operating at various levels. Sleep deprivation or restriction of different magnitude is becoming an integral component of our daily life in the current civilization some of which are also reflected in our cognitive functioning including lapses in attention, anxiety, memory impairment etc. The assessment of brain activity through high resolution EEG system is commonly employed for stochastic evaluation of the EEG dynamics to decipher functional properties of the neural networks

during reduced sleep. Though, a global increase in the delta power after acute sleep deprivation is considered a gold standard for detecting the homeostatic drive, the spectral analysis of EEG time series and spatial properties of the EEG spectrum appear promising in deciphering the neural network properties after acute or chronic sleep loss. The local and global features of the crucial neural networks after the acute and chronic sleep loss are highlighted to make an understanding of the role of EEG dynamics in sleep homeostasis.

Symposium 10 (S10)

Abs.S10.1

A Look at Interactions between Emotion and Attention using ERPs

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Recent studies investigating the relationship between emotion and attention have shown reciprocal relationships between them. Broad scope of attention is linked to happy expressions and narrow scope of attention is linked to sad expressions. Given these links between emotion and attention, we performed two studies using emotional stimuli investigating shifts in attention and executive control. We also explored hemispherical asymmetries. Shifts of attention were studied using the phenomenon of inhibition of return (IOR) using a exogenous cue paradigm with schematic happy and sad emotional target faces. Reaction times and ERPs were measured. Results revealed reduced IOR for left compared to right visual field with sad faces but no such asymmetry for happy faces. Cued N1 amplitudes were suppressed for happy targets but not for sad targets presented to the left visual field. Nd amplitudes were enhanced for right-hemispheric sad faces especially with object-based IOR. The results indicate right-hemispheric advantage in the capture of attention by negative emotion especially with object-based selection.

Executive control was studied using a flanker task with happy and threatening faces. Results showed hemispheric asymmetries in the flanker interference effect with larger flanker effect in the right hemisphere for threatening faces and in the left hemisphere for happy faces. Happy faces were processed faster compared to threatening faces as indicated by increased N100 amplitudes and faster RTs. In addition, error related negativity magnitudes were dependent on the emotional content. These studies show changes in ERPs indicating differences in attentional processes as a function of emotional content.

Abs.S10.2

Brain Basis of the Capacity Limits of Information Processing

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Background : The human brain has immense capacity for parallel processing of information. The possibility for simultaneous processing of large amounts of information is constrained by capacity limitations of attention/working memory. This capacity which was earlier set at 7 bits of information is now found to be 4 bits of information. The brain basis of the capacity limitation needs to be ascertained. Further the process of chunking may increase the capacity limit.

Aim : The present study aimed to answer whether the brain basis of this capacity limit could be located to the networks of attention/ working memory/perception.

Method : Three studies were conducted to study the capacity limitation with visual displays of words, digits and figures. Each type of stimulus was displayed under two conditions. The chunked condition had stimuli which favored chunking through arrangement of the stimuli. In the non chunked condition the stimuli were arranged randomly and hence did not favor chunking.

Sample : In each of the three studies 20 normal healthy right handed college educated volunteers of both participated after giving informed consent.

EEG Recording : Surface EEG was recorded from 28 channels with horizontal and vertical eye movements being recorded from four channels. The stimulus appeared for 200 ms followed by a probe after 500 ms. The probe either matched or did not match the stimulus. The subject pressed a button to indicate whether the probe matched the stimulus or not.

Results : The accuracy was high across the 3 tasks. P300 component appeared after the stimulus. In some of the tasks a prolonged positivity appeared. The distribution of the P3 differed across the 3 tasks. The effects of chunking and of matched probe would be discussed in the presentation.

Abs.S10.3

Biomarkers for Neurodegenerative Disorders using State-of-the-Art Multi-Modal Imaging Modalities : Detection and Mapping of Anti-oxidant Marker 'Glutathione'

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Glutathione (GSH) serves as an important anti-oxidant in the brain by scavenging harmful reactive oxygen species that are generated during different molecular processes. The GSH level in the brain provides indirect information on oxidative stress of the brain. We report in vivo detection of GSH non-invasively from various brain regions (frontal cortex, parietal cortex, hippocampus and cerebellum) in bilateral hemispheres of healthy male and female subjects and patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients. All AD patients who participated in this study were on medication with cholinesterase inhibitors. Healthy young male (age 26.4±3.0) and healthy young female (age 23.6±2.1) subjects have higher amount of GSH in the parietal cortical region and a specific GSH distribution pattern (parietal cortex> frontal cortex >hippocampus ~cerebellum) was found. Overall mean GSH content is higher in healthy young female compared to healthy young male subjects and GSH is distributed differently in two hemispheres among male and female subjects. Both young female and male subjects, statistically significant (P=0.02 for young female and P=0.001 for young male) difference in mean GSH content is found when compared between left frontal cortex (LFC)

and right frontal cortex (RFC). In healthy young female subjects, we report statistically significant correlation (positive) of GSH content between RFC and LFC (r=0.641, P=0.004) as well as right parietal cortex (RPC) and left parietal cortex (LPC) (r=0.797, P=0.000) regions. In healthy young male subjects, statistically significant correlation (positive) of GSH content was observed between LFC and LPC (r=0.481, P=0.032) regions. The difference in mean of GSH content between healthy control young female and female patients in RFC region (P=0.003) and difference in mean of GSH content in control healthy young male and male patients (P=0.05) in LFC region is found to be statistically significant.

Abs.S10.4

Realization of Delayed Intention : An Electrophysiological Approach

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Prospective memory (PM) involves forming an intention and then realizing it at some appropriate time or in response to some external cue in the future (Harris, 1984). In this talk, I will discuss the processes underlying the encoding and performance of future intentions and planned actions in the context of event-related brain potentials (ERPs) to explore the neural activity associated with the formation and realization of an intention. ERPs have been used to examine the temporal dynamics of the neural processes underlying prospective memory. Modulations of the ERPs elicited during prospective memory have been associated with the detection of prospective cues and the retrieval of intentions from memory.

Greater negativity over the frontal-polar region was associated with intention formation trials in which the intention was later realized. On PM cue trials, N300 was associated with the detection of a cue. A late positive complex was observed that might have reflected the retrieval of an intention from memory, and a frontal slow wave was observed that might have reflected the activity of a neural system that supported disengagement from the ongoing activity when the cue was detected. The N300 is greater in amplitude for prospective hits (i.e., prospective cues that elicit a prospective response) than prospective misses (i.e., prospective cues that fail to elicit a prospective response) or ongoing activity trials, leading to the suggestion that this modulation of the ERPs is associated with the detection of prospective memory cues.

The prospective positivity reflects a sustained positivity over the parietal region between 500 and 1000 ms after stimulus onset (West et al., 2001). There is evidence that the P3b component contributes to the prospective positivity. The later portion of the prospective positivity (between 600 and 800 ms) is also greater in amplitude when there are multiple cue-intention associations relative to when there is a single cue-intention association (West et al., 2003b), leading to the proposal that the prospective positivity is associated with the activity of a neural mechanism that supports the retrieval of an intention from memory (West & Ross-Munroe, 2002). Overall, the talk will delineate progress towards understanding realization of delayed intention by using of electrophysiological method.