

The 27th Annual Winter Neuropeptide Conference



January 28th-31st, 2006
Breckenridge, Colorado

The International Neuropeptide Society is Pleased to Announce The
27th Annual Winter Neuropeptide Conference
Beaver Run Resort and Conference Center
January 28th – 31st, 2006

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** Oldest Neuropeptide
Conference in North
America.

**WELCOME TO THE ANNUAL WINTER NEUROPEPTIDE
CONFERENCE.**

We are pleased to be hosts for this, the twenty-seventh year of the conference.

We hope that your meetings are profitable and your stay in Breckenridge relaxing and enjoyable. If we can be of any assistance, just let us know.

Cordially,

Deb Edwards

Deb Edwards
Conference Coordinator



 Sponsors

The Winter Neuropeptide Conference would like to acknowledge and thank the following company for the financial support of the 2005 conference:

Johnson & Johnson Pharmaceutical Research & Development

*The Winter Neuropeptide Conference is an affiliate of the International
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 Acknowledgements

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Hearthstone Restaurant

Breckenridge Ski Resort

Schedule-at-a-Glance

Registration – 1st Floor South Foyer of the Conference Center
All symposia meetings will be held in Peak 17, 1st Floor Conference Center

Saturday, January 28

3 – 7 PM	Registration/Check-in Desk Open
4:45 PM	Welcome and Opening Remarks
5 – 7 PM	Symposia Meeting (Beverages & Light Refreshments Provided)

Sunday, January 29

3 – 10 PM	Registration/Check-in Desk Open
4 – 6 PM	Symposia Meeting (Beverages & Light Refreshments Provided)
6 – 8 PM	Dinner Break (on your own)
8 – 10 PM	Symposia Meeting (Beverages Provided)

Monday, January 30

3 – 10 PM	Registration/Check-in Desk Open
4 – 6 PM	Symposia Meeting (Beverages & Light Refreshments Provided)
6 – 8 PM	Dinner Break (on your own)
8 – 10 PM	Symposia Meeting (Beverages Provided)

Tuesday, January 31

4 – 6 PM	Registration/Check-in Desk Open
4:30 – 6:00 PM	Symposia Meeting (Beverages & Light Refreshments Provided)
7 PM	Dinner at The Hearthstone Restaurant (Additional fee and registration required)

**The International Neuropeptide Society is pleased to
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**The 27th Winter Neuropeptide Conference
Breckenridge, Colorado
January 28 - 31, 2006**

Program Chairs: John Quinn and Andy Russo; *Treasurer and Facilities Chair:* Curt Sandman; *Young Investigator Chair:* Doug Brenneman; *Steering Committee Members:* Bill Flynn, Joanna Hill-Devine, Catherine Spong, Fleur Strand

Saturday, January 28, 2006

4:45 PM Welcome and opening remarks

5:00 - 7:00 PM Autism Joanna Hill-Devine, National Institutes of Health

- **The role of the vasopressin receptors in the regulation of social behavior.** Scott Wersinger, University of Buffalo, Buffalo, NY
- **Social behavior and vasopressin 1a receptor microsatellites.** Elizabeth Hammock, Vanderbilt University, Nashville, TN
- **Reduced vasoactive intestinal peptide generates deficits in social behavior.** Joanna Hill-Devine, National Institutes of Health, Bethesda, MD

Sunday, January 29, 2006

4:00 - 6:00 PM **Stem Cells.** Mark Howard, Smith & Nephew Research Centre

- **Clinical Relevance of the Stem Cell: A Surgeon's Tool.** Mark Howard, Smith & Nephew Research Centre, York, UK
- **Neuropeptide Y and Hippocampal Neurogenesis.** Liam Gray, Southampton University, Southampton, UK
- **Functional neurons derived from transdifferential human mesenchymal stem cells.** Pranela Rameshwar, New Jersey Medical School, Newark NJ
- **Regulation of the expression of the substance P encoding gene, prepro-tachykinin A, by REST isoforms.** John Quinn, University of Liverpool, Liverpool, UK

6:00 - 8:00 PM **Dinner Break** (on your own)

8:00 - 10:00 PM **Intranasal Delivery.** Mike Kubek, Indiana University School of Medicine

- **Nasal delivery of NAP: a neuroprotective peptide in phase I clinical trials.** Illana Gozes, Tel Aviv University, Tel Aviv, Israel
- **Intranasal neuropeptides bypass the blood-brain barrier to target the CNS and reduce systemic exposure.** William Frye II, Alzheimer's Research Center Regions Hospital, University of Minnesota, St. Paul, MN
- **Characterization of Novel Intranasal Sustained-Release Nanoparticles for Delivery of Neuropeptides to the Brain.** Mike Kubek, Indiana University School of Medicine, Indianapolis, IN
- **Exploring drug size and dose response for nose to brain delivery.** Beth Hill, Stanford University School of Medicine, Stanford, CA

Monday, January 30, 2006

4:00 - 6:00 PM Sepsis. Ken Becker

- **Overview of CT-Peptides and its regulation.** Andy Russo, University of Iowa, Iowa City, IA.
- **Hormokines – a novel concept in neuro-endo-immunology.** Beat Müller, University Hospital, Basel, Switzerland
- **Clinical use of neuropeptides for risk stratification in sepsis.** Mirjam Christ-Crain, Barts and the London Medical School, London, UK
- **Calcitonin Peptides as a novel therapy in Sepsis.** Eric Nylen, Bethesda, MD

6:00 - 8:00 PM Dinner Break (on your own)

8:00 - 10:00 PM Epilepsy & Neuroprotection. Mike Kubek, Indiana University and Illana Gozes, Tel Aviv University

- **Overview VIP/ADNP/NAP regulation and function.** Illana Gozes, Tel Aviv University, Tel Aviv, Israel
- **Dynamic regulation of gene expression during epilepsy.** Anja Kipar, University of Liverpool, Liverpool, UK
- **Novel Characteristics Related to the Anticonvulsant Mechanism of TRH (Protirelin).** Mike Kubek, Indiana University School of Medicine, Indianapolis, IN
- **NAP influences immune mediated responses: implications for autoimmune diseases.** David Pozo Perez, University of Seville Medical School, Seville, Spain

Tuesday, January 31

4:30 - 6:00 PM Virus & Peptide Interaction. James Stewart, University of Liverpool

- Tachykinin regulation of the immune **response in virus infection in the lung.**
James Stewart, University of Liverpool, Liverpool, UK
- **Clinical Update on Peptide T: The First CCR5 Entry Inhibitor.** Candace Pert & Michael Ruff, Georgetown University, Potomac, MD
- **TBD**

7:00 PM Dinner at Hearthstone Restaurant (additional fee and registration required)

Session 1: Neuropeptides and Autism

Joanna M. Hill

Laboratory of Behavioral Neuroscience
National Institute of Mental Health, NIH
Bethesda, MD, 20892

Autism is a neurodevelopmental disorder recognized early in childhood that is more prevalent in males and is characterized by deficits in social behavior, deficits in language and communication, and rigid and stereotypical behavior patterns. An animal model expressing the behavioral aspects of autism would be useful in understanding this disorder that is thought to originate prenatally.

Following a brief description by Dr. Joanna Hill of the salient features of autism and a description of desirable characteristics of a model of autism, we will explore the role of select neuropeptides implicated in the regulation of social behavior.

In the late 1980's the relationship between the hypothalamic neuropeptides oxytocin and vasopressin and social behavior was beginning to be recognized. Subsequent studies revealed actions of these neuropeptides in the expression of the social interactions involved in affiliation, aggression, sexual behavior and parental behavior. Much current research is focused on vasopressin receptor subtypes. The first speaker, Dr. Scott Wersinger, will describe his studies characterizing the social behavior of vasopressin 1b receptor null mice. Dr. Elizabeth Hammock will then discuss her studies of microsatellite polymorphisms in the vasopressin 1a receptor gene and their relation to anxiety and social behavior in prairie voles.

Vasoactive intestinal peptide (VIP) is an important regulator of embryonic growth and development during the early postimplantation period characterized by neural tube closure and neurogenesis that is the period during which the pathological changes characteristic of autism are thought to be initiated. Dr. Joanna Hill will describe recent studies of two mouse models linking prenatal deficiencies in VIP to deficits in social approach and preference for social novelty in adult mice.

THE ROLE OF THE VASOPRESSIN 1b RECEPTOR IN THE REGULATION OF SOCIAL BEHAVIOR

Scott R. Wersinger¹, Heather K. Caldwell², and W.S. Young²

¹Department of Psychology, SUNY, Buffalo, NY.

²Section on Neural Gene Expression, NIMH, NIH, Bethesda, MD

Autism spectrum disorder is characterized by a constellation of symptoms that vary in their manifestation and severity. Since autism spectrum disorder is likely to be a “brain” disease, involving virtually every brain region and neurotransmitter system, it has proven difficult to develop an animal model that fully approximates it. An alternative strategy is to develop models that mimic a specific facet of the disorder and gain a mechanistic understanding of individual symptoms. One hallmark diagnostic criterion is a profound deficit in social behavior. We have characterized a mutant mouse model in which social behavior is reduced and believe this may be a promising tool for understanding some of the factors that contribute to the social deficits observed in autism spectrum disorder. Mice lacking the vasopressin 1b receptor (*Avpr1b*) gene are markedly less aggressive towards conspecifics than are wild-type mice. However, predatory behavior is intact. This is a critical contrast because it shows that the mutant mice are capable of detecting and responding normally to external sensory cues in some situations. However, when it comes to responding to social cues, the mutants do not respond normally. We have conducted a battery of sensory tests (with a focus on olfaction), and do not find that a sensory deficit is the mechanism behind our phenotype. While the mutant mice have normal olfaction they do not show the normal preference for soiled bedding over clean bedding or female-soiled bedding over male-soiled bedding. Our evidence indicates that the mutants can detect social cues; however, they do not respond to them as a normal mouse does. Our data suggest the serotonin system is altered by disruption of the *Avpr1b* gene. Our current research is focusing on further elucidating the neural mechanism by which disruption of the *Avpr1b* gene reduces social motivation, including characterizing the serotonergic system as well as hippocampal function in the mutants.

REPEAT DNA AND SOCIAL BEHAVIOR: THE VASOPRESSIN 1a RECEPTOR

Elizabeth A.D. Hammock¹ and Larry J. Young²

¹John F. Kennedy Center for Research on Human Development, Department of Pharmacology, Vanderbilt University, Nashville, TN 37232

²Center for Behavioral Neuroscience, Yerkes National Primate Research Center, Department of Psychiatry, Emory University, Atlanta, GA 30329

Social behavior traits vary dramatically between and within species. Neuroethological and neurobiological studies of social behavior in vole species have revealed potential neural and genetic mechanisms generating such diversity. Socially monogamous prairie voles and asocial montane voles differ in their brain distribution patterns of the vasopressin 1a receptor (V1aR). Site-specific pharmacological manipulation and viral vector gene transfer of the V1aR in voles demonstrate a causal role of V1aR distribution patterns. These patterns of V1aR expression appear to be regulated in part by a repetitive sequence (microsatellite DNA) in the 5' non-coding region of the gene encoding V1aR (*avpr1a*). Compared to the montane vole, the prairie vole has a highly expanded microsatellite at this locus. In transcription reporter assays in cell culture, species differences in microsatellite length modify gene expression levels, allowing for the possibility that species differences affect gene expression in vivo. Microsatellite DNA is particularly interesting due to its high levels of polymorphism as a result of its relatively high mutation rates. This high level of mutation, in combination with its potential to regulate gene expression, suggests a rapid mechanism for generating diverse behavioral phenotypes. Specifically, rapid expansion and contraction of non-coding repeat DNA could alter a gene expression patterns and potentially result in differential engagement and/or development of neural circuits. In further support of this hypothesis, prairie voles demonstrate significant variability in social behavior traits, V1aR distribution patterns and microsatellite length. Genetic selection for microsatellite length at the *avpr1a* locus in prairie voles demonstrates that intra-specific variation in microsatellite length predicts individual differences in V1aR distribution patterns and sociobehavioral traits. In vitro transcription reporter assays indicate that intra-specific variation in microsatellite length also modifies gene expression, indicating that the microsatellite likely plays a causal role. A similar microsatellite locus in the primate *avpr1a* gene may play a role in the diversity of social behaviors within and between primate species as well.

REDUCED VASOACTIVE INTESTINAL PEPTIDE GENERATES DEFICITS IN SOCIAL BEHAVIOR

Joanna M. Hill¹, Katrina Cuasay¹, Maria Lim¹, Madeleine Stone¹, Sandra Y. Flores¹, Irit Spivak-Pohis², Daniel Abebe³, Illana Gozes², Victor May⁴, James Waschek⁵

¹Laboratory of Behavioral Neuroscience, NIMH, NIH, Bethesda, MD, USA

²Department of Clinical Biochemistry, Sackler School of Medicine, Tel Aviv, Israel.

³Laboratory of Developmental Neurobiology, NICHD NIH, Bethesda, MD, USA

⁴Department of Anatomy and Neurobiology, Univ. Vermont, Burlington, VT, USA

⁵Department of Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA, USA

Autism is a neurodevelopmental disorder characterized by deficits in social behavior. It is more prevalent in males and is thought to originate prenatally. Maternal vasoactive intestinal peptide (VIP) regulates early postimplantation growth and development during embryonic (E) days 8-11 in the mouse. Blockage of VIP during this period results in developmental delays in neonates and atypical social responses in open field testing of adults. In the current studies, social approach and preference for social novelty were examined in two groups of mice that had experienced reduced VIP during prenatal development. One group experienced blockage of VIP through treatment of pregnant mice with a VIP antagonist from E8-10. Control pregnant females received saline. In the second group, VIP/PHI genes were disrupted by homologous recombination resulting in VIP-deficient mice. The offspring of VIP-deficient VIP +/- mothers were compared with the offspring of VIP ++ mothers (controls) to assess the effect of reduced maternal VIP on social behavior. VIP levels assayed in the brains of VIP +/- mice were found to be approximately 50% of the levels found in wild type mice. Mice were tested as adults and male mice from both groups exhibited significantly reduced social approach and an absence of preference for social novelty compared with control male mice. Among the offspring of VIP +/- mothers, all males exhibited significant deficits, regardless of their genotype. Female mice treated with a VIP antagonist during embryogenesis showed no deficits in social tasks compared with control females. Also, female VIP ++ offspring of VIP +/- mothers did not differ from control females; however, female VIP +/- and VIP -/- mice exhibited deficits in social approach and preference for social novelty. These data indicate that maternal levels of VIP can have important consequences on the social behavior of adult offspring and that male offspring are more susceptible than female offspring to the deleterious effects of reduced VIP during development. The reduced social approach and lack of social preference of female VIP +/- and -/-, but not ++ offspring of VIP +/- mothers, indicates that VIP genotype has consequences on adult social behavior. In male mice, the genotypic effects are apparently masked by the potent effect of lower maternal levels of VIP. The deficits in social behavior in these experimental paradigms indicate their potential use as models for aspects of neurodevelopmental disorders such as autism. *Support Contributed By: NIMH IRP*

Session 2: Stem Cells

Clinical Relevance of the Stem Cell: A Surgeons Tool

Mark R Howard

Stem cell-based technologies have received enormous scientific attention due to their potential in delivering novel therapeutic applications. The aim of cell therapy is to replace, repair or enhance the function of damaged tissues or organs. There are many considerations in the practical clinical use of autologous or allogeneic sources of stem cells ranging from defining the required concentration for the efficacy of the therapy to deducing the optimal cell source. Within a few years the likelihood of utilising adult stem cells as a possible cell source have increased substantially, having been isolated from numerous adult tissues and demonstrated the potential to differentiate into tissues other than their tissue of origin. Smith & Nephew are playing a major role in the development of cell-based therapies and continue to search for potential academic collaborations to facilitate the clinical relevance of the stem cell.

FUNCTIONAL NEURONS DERIVED FROM TRANSDIFFERENTIATED HUMAN MESENCHYMAL STEM CELLS

Steven J. Greco, Kathy Trzaska, Nitixa Patel, Pranela Rameshwar

Data will be presented to show potential application for adult human bone marrow mesenchymal stem cells (hMSC). Applications include, but are not restricted to drug abuse, Parkinson's disease, spinal cord injury, traumatic brain injury and psychiatric disorders. The studies are intended to employ material science and engineer to translate the biology of the adult stem cells to patients. We have developed in vitro models to identify the stage at which hMSCs could be implanted at a site of tissue injury, in vivo as undifferentiated, partly or fully transdifferentiated neurons. hMSC-derived neurons are used as a model to determine how the developing neurons could be influenced by factors at the site of injury. Data will be presented on two genes: Tac1, which encodes the neurotransmitter substance P, and REST, a silencer of neural-specific genes in non-neural cells. The Tac1 gene undergoes developmental regulation as hMSCs mature into neurons. This regulation occurs at two levels, transcription and translation. Transcriptional regulation occurs by the removal of REST on the Tac1 gene, leading to decrease gene transcription as hMSC mature into functional neurons. Translational regulation of the Tac1 mRNA (PPT-A) is currently being addressed in studies with miRNA arrays. The prototypical microenvironmental factor, IL-1a affects the expression of specific miRNAs in the developing neurons, thereby affecting the synthesis of the neurotransmitter substance P. IL-1a has been shown to induce the synthesis of substance P. This effect is specific since similar effect was not demonstrated for another cytokine, IL-2. The significance of these effects relates to premature expression of the Tac1 gene in developing neurons, by IL-1a, or the blunted synthesis of the neurotransmitter substance P by IL-2. Overall, the studies have begun to unravel novel methods on mechanisms by which hMSC-derived neurons could be affected by factors within the microenvironment of injured sites. The potential for neurons to undergo premature synthesis of neurotransmitters, or blocking of neurotransmitters, will open new paradigms, bringing stem cell therapy for neural disorders closer to translational medicine.

REGULATION AND FUNCTION OF DISTINCT ISOFORMS OF THE REST TRANSCRIPTION FACTOR IN REGULATION OF NEUROPEPTIDES

Eleanor Spencer, Kate Haddley, Mark Howard, Jill Bubb and John Quinn.

Neurotransmitter Biology Group, Physiology Department, University of Liverpool, jquinn@liv.ac.uk

Neural stem cells (NSCs) have been the subject of intense study over recent years due to their therapeutic potential and their use as a tool to unravel the molecular mechanisms underlying neurogenesis. Understanding the mechanisms by which neural stem cells differentiate into neurons is key to our unlocking this potential. The transition from neural stem cell to neuron is accompanied by wholesale changes in gene expression patterns ultimately resulting in transcriptional activation of cohorts of pan-neuronal and subtype specific genes. Recent evidence has suggested that the RE1 silencing transcription factor (REST) may be involved (also termed Neuronal Restrictive Silencer Factor, NRSF); however the actual function of REST in neural stem cells is still poorly understood. REST it would appear is required for differentiation of adult hippocampal stem cells into neurons. Similarly little is known about REST in mature neurons of the adult brain where it has been found to be expressed in select populations. Originally, REST was proposed as a silencer of neuronal gene expression in non-neural tissue; however it is becoming increasingly clear that REST has multiple actions that vary according to cell type and developmental stage. We have been addressing the action of REST in adult neurons, cancer and more recently in MHP36 embryonic hippocampal stem cells. We will present data that not only is the regulation of expression of full length important but a crucial feature is the expression of a splice variant that encodes a truncated REST variant termed REST4 in the rodent and sNRSF in the human. We have explored REST function by its ability to regulate the expression of the substance P and AVP neuropeptides.

Session 3: Intranasal Delivery

INTRANASAL NEUROPEPTIDES BYPASS THE BLOOD-BRAIN BARRIER TO TARGET THE CNS AND REDUCE SYSTEMIC EXPOSURE

William Frey II

Alzheimer's Research Center Regions Hospital, University of Minnesota, St. Paul, MN

We have developed a non-invasive, intranasal method of bypassing the blood-brain barrier to deliver neuropeptides to the brain and spinal cord. This method allows drugs that do not cross the blood-brain barrier to be delivered to the central nervous system and eliminates the need for systemic delivery, thereby reducing unwanted systemic side effects. Delivery from the nose to the central nervous system occurs within minutes along both the olfactory and trigeminal neural pathways. Delivery occurs by an extracellular route and does not require that the drugs bind to any receptor or undergo axonal transport.

IGF-I has been delivered to the brain and spinal cord by this route [Thorne (2004) *Neuroscience* 127:481-496.] Intranasal IGF-I given up to four hours after stroke markedly reduces infarct volume and improves neurological function [Liu (2004) *Journal of Stroke and Cerebrovascular Diseases* 13(1): 16-23.] Intranasal NGF has been shown to successfully treat Alzheimer's disease in a transgenic mouse model. [Capsoni (2002) *PNAS* 99(19):12432-12437 and De Rosa (2005) *PNAS* 102(10): 3811-3816.] Intranasal neurotrophins have also been shown to stimulate neurogenesis in adult animals [Jin (2003) *Ann Neurol* 53:405-409]. Finally, Gozes has used intranasal delivery to target NAP and ADNF to the brain to treat anxiety and neurodegeneration. [Alcalay (2004) *Neuroscience Letters* 361: 128-131; Gozes (2000) *JPET* 293(3): 1091-1098.]

The peptide hypocretin-1 is intranasally targeted to the brain and spinal cord [Hanson (2004) *Drug Delivery Technology* 4(4):66-71]. Banks has demonstrated that intranasal exendin is delivered directly to the brain and improves memory, cognition and neuronal survival [Banks (2004) *JPET* 309:469-475 and during (2003) *Nature Med.* 9:1173-1179]. Proteins such as interferon beta-1b, have been intranasally delivered to the central nervous system [Ross et al. (2004) *J Neuroimmunol* 161:66-77].

Intranasal delivery of neuropeptides to the CSF in humans has been documented by Born (2002) *Nature Neuroscience* 5(6): 514-516. Intranasal insulin improves memory and mood in healthy adults [Benedict (2004) *Psychoneuroimmunol.* 29:1326-1334] and improves memory in patients with Alzheimer's disease without altering blood levels of insulin or glucose [Reger (2005) *Neurobiology of Aging* in press.] Intranasal oxytocin has been found to increase trust in humans following direct delivery from the nose to the brain (Kosfeld (2005) *Nature* 435:673-676.)

Intranasal leptin reduces food consumption and body weight in animals [Schulz (2004) *Endocrinol* 145:2696] and reduces appetite [Shimizu (2005) *Int. J. Obesity* 29:858] while intranasal PYY has been claimed to do the same in humans. Intranasal insulin reduces body fat in men [Hallschmid (2004) *Diabetes* 53:3024-3029].

CHARACTERIZATION OF NOVEL INTRANASAL SUSTAINED-RELEASE NANOPARTICLES FOR DELIVERY OF NEUROPEPTIDES TO THE BRAIN

M. J. Kubek¹, M. Yard¹, D. K. Lahiri¹, and A. J. Domb²

¹Indiana University School of Medicine, Indianapolis, IN, 46202 USA

²Hebrew University of Jerusalem, Jerusalem, 91120 Israel

The neuropeptides represent a rapidly-expanding class of potential new CNS drugs. Unfortunately, delivery of neuropeptides directly to specific brain sites has been a major obstacle in their therapeutic development. Rapid metabolism in all tissue compartments and a lack of blood brain barrier penetration are the two most daunting issues related to neuropeptide sustained bioavailability. Interestingly, the only nerves in direct contact with the external environment are primary olfactory neurons. This unique neuroanatomical relationship presents a means to limit metabolism and bypass the blood brain barrier to enhance direct access to olfactory neuronal transport mechanisms to specific temporal lobe sites. Advantages of this non-invasive CNS gateway include: ease of use in dosing and treatment schedules, long-term compliance, and uninterrupted delivery. However, several transolfactory barriers exist. Solutes entering the nasal cavity are destined for three regions: 1) vestibular; 2) respiratory and 3) olfactory. The olfactory region is the most functionally important site for direct access to the brain. Three major barriers to neuropeptide bioavailability exist in this region: 1) presence of tight junctions between sensory and supporting cells, preventing epithelial transport to the submucous space; 2) a mucous layer containing protective proteolytic/hydrolytic enzymes that impart an enzymatic barrier to nasally administered drugs and peptides and; 3) mucous layer clearance that influences time-dependent neuropeptide absorptive (uptake) availability. Following olfactory neuronal uptake, neuropeptides are susceptible to further degradation during anterograde transneuronal transport as they are carried by axonal microtubules of the olfactory tract to primary CNS structures; namely amygdala, hippocampus, piriform, and entorhinal cortices. Next, sufficient sustained neuropeptide release at these targets is necessary for a pharmacological effect. The development of newer surface-eroding nanoparticle carriers provides a means to exploit this delivery pathway. Intranasal application of surface-eroding neuropeptide-coupled polyanhydride nanoparticles would enhance: 1) olfactory nerve uptake; 2) transneuronal transport; and 3) site-specific release of neuropeptides in temporal lobe targets. Disorders such as depression, epilepsy, dementia and focal stroke, among others related to the temporal lobe, would be potentially treatable by intranasal neuropeptides. We reported previously that site-specific delivery of the neuropeptide Protirelin, fabricated as a polyanhydride microdisk, can inhibit partial and generalized seizures *in vivo*, indicating that when localized to sites in the temporal lobe it can affect local excitability. Additionally, we have also developed a method to screen biodegradable nanoparticle neuropeptide carriers for toxicity and bioactivity *in vitro*. This methodology should expedite the development of polyanhydride-based sustained-release carriers for intranasal therapeutic neuropeptides.

Session 4: Neuropeptides and Sepsis

Chair: Prof. Ken Becker

Prof. Andy Russo, "Overview of CT-Peptides and its regulation"

Prof. Beat Müller, Hormokines – a novel concept in neuro-endo-immunology

Dr. Mirjam Christ-Crain – Clinical use of neuropeptides for the risk stratification in sepsis

Prof. Eric Nylen – Calcitonin Peptides as a novel therapy in Sepsis

OVERVIEW OF THE CALCITONIN PEPTID

Andrew F. Russo

Dept. Physiology and Biophysics, University of Iowa

It has been over 40 years since the discovery of the peptide hormone calcitonin (CT). In the ensuing years, CT has been in and out of the scientific limelight. After its initial fame, it was realized that the hypocalcemic activity of CT, for which it was discovered and named, is not essential under normal conditions. The other members of a troika of calcium-regulating hormones, vitamin D3 and parathyroid hormone, can fully compensate for an absence or excess of CT. Nonetheless, CT is an effective therapeutic for certain types of osteoporosis and Paget's disease. In the early 1980's, CT returned to a prominent position when it was unexpectedly found to harbor a novel neuropeptide, termed calcitonin gene-related peptide (CGRP) that was generated by neural-specific alternative RNA processing. The mechanism underlying this processing remains elusive, but most likely involves cell-specific factors that "define" the CT specific exon within the CT/CGRP transcript. Once the splicing choice is established, all regulation of CT/CGRP gene expression appears to occur exclusively at the transcriptional level. Abnormal CGRP levels have been observed in several pathological conditions, mostly involving the neurovasculature. Recently, CGRP has been shown to be both sufficient and necessary for migraines. Promoter studies have revealed cell-specific and hormone-responsive elements that control the CT/CGRP gene. Interestingly, the gene is stimulated by cytokines and other agents that activate MAP kinases. This may contribute to the widespread overexpression of pro-CT that is seen in sepsis. Indeed, it is the possible role of the pro-CT peptide in septic shock that has brought CT back to the limelight and will be the focus of this session

PRO-ADRENOMEDULLIN PREDICTS SEVERITY AND OUTCOME IN COMMUNITY-ACQUIRED PNEUMONIA

Mirjam Christ-Crain, Nils Morgenthaler, Joachim Struck, Daiana Stolz, Roland Bingisser, Christian Müller, Andreas Bergmann, Michael Tamm and Beat Müller

Department of Internal Medicine, University Hospital Basel, Switzerland
Division of Pneumology, University Hospital Basel, Switzerland
Research Department, Brahms AG, Hennigsdorf, Germany.

Background: Pro-adrenomedullin (proADM), the more stable mid regional fragment of adrenomedullin, is helpful for individual risk assessment and outcome prediction of sepsis. The major cause of sepsis is community-acquired pneumonia (CAP). We investigated the value of proADM levels for severity assessment and outcome prediction in CAP.

Methods: Data from 302 patients admitted to the emergency department with CAP were included. ProADM levels were measured with a new sandwich immunoassay (Brahms Sevadil® LIA, Hennigsdorf/Berlin, Germany).

Results: ProADM levels, in contrast to C-reactive protein and leukocyte count, increased with increasing severity of CAP, classified according to the PSI score (p ANOVA <0.001). In patients who died during follow-up, proADM levels on admission were significantly higher as compared to levels in survivors (2.1 [1.5-3.0] vs. 1.0 [0.6-1.6] nmol/L, p<0.001). In a receiver operating characteristic (ROC) analysis for survival the area under the ROC curve (AUC) for proADM was 0.76 (95% confidence interval [CI] 0.71-0.81), which was significantly better as compared to procalcitonin (p = 0.004), C-reactive protein (p < 0.001) and total leukocyte count (p = 0.001) and similar to the AUC of the PSI (0.73, p=0.54).

Conclusions: ProADM, as a novel biomarker, is a useful tool for the risk stratification of patients with CAP.

COPEPTIN, A PRECURSOR OF VASOPRESSION, AS A PROGNOSTIC MARKER IN SEPSIS — AN OBSERVATIONAL STUDY

Mirjam Christ-Crain, Nils G. Morgenthaler, Joachim Struck, Andreas Bergmann,
and Beat Müller

Department of Internal Medicine, University Hospital Basel, Switzerland
Research Department, Brahms AG, Hennigsdorf/Berlin, Germany

Background & Aim: The response of the hypothalamo-pituitary-adrenal axis to stress is mediated mainly through corticotrophin-releasing hormone and vasopressin. Accordingly, vasopressin levels are increased in septic shock. However, measurement of vasopressin is difficult because of its instability and short half-life. Copeptin is a more stable peptide derived from the same precursor molecule. This study aims to evaluate copeptin levels and its prognostic value in a prospective observational study of 101 consecutive critically ill patients, as compared to 50 healthy controls.

Methods: Copeptin was measured in the serum of all patients with a newly developed sandwich immunoassay.

Results: On admission, 53 patients had sepsis, severe sepsis or septic shock and 48 had systemic inflammatory response syndrome (SIRS). Copeptin levels correlated with basal cortisol levels ($r=0.40$, $p<0.001$). Median (range) copeptin values on admission in pmol/l were in patients with SIRS 27.6 (2.3-297), with sepsis 50.0 (8.5-268), with severe sepsis 73.6 (15.3-317) and in patients with septic shock 171.5 (35.1-504), as compared to 5.0 (1.5-30.3) in healthy controls (p for all comparisons versus controls <0.001). On admission, circulating copeptin levels in patients with sepsis, severe sepsis or septic shock were higher in non-survivors (171.5, 46.5-504.0) as compared to survivors (86.8, 8.5-386.0, $p=0.01$). In a receiver operating curve (ROC) analysis for the survival of patients with sepsis, the AUC for copeptin was 0.75 (95%CI 0.64-0.82). In comparison, the AUC for CRP was 0.55 (0.44-0.65, $p=0.02$), for basal cortisol 0.60 (0.49-0.69, $p=0.08$) and for the APACHE II score (0.71, 0.61-0.80, $p=0.78$).

Conclusions: Copeptin levels are elevated in sepsis, correlate with stress-induced cortisol levels and might provide a useful new tool for an individual risk assessment of septic patients. The availability of a reliable assay for the measurement of vasopressin could also prove useful for the assessment of fluid status in various diseases.

Session 5: Epilepsy & Neuroprotection

THYROTROPIN-RELEASING HORMONE (TRH): A NOVEL GLUTAMATE MODULATOR AND ITS INTRANASAL DELIVERY TO SEIZURE FOCI

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Generalized seizures induce substantial and prolonged increases in TRH levels selectively in the amygdala, piriform, hippocampal and entorhinal cortex, and in specific neocortical loci. This response is preceded temporally by a dramatic upregulation of TRH mRNA in specific neuronal populations such as granule cells of the hippocampal dentate gyrus in an activity dependent manner. Moreover, these same neurons constitutively express TRHR1 and metabotropic glutamate receptor mRNA's and data indicate that TRH release is enhanced postictally in association with a prolonged down-regulation of TRH receptors. Pharmacologically, TRH is known to have antiepileptic and antiepileptogenic effects in several seizure paradigms including kindling. Taken together, these data provide evidence that in epileptic tissue TRH is co-released with glutamate and functions as an endogenous neuroprotectant. However, its mechanism of action is unclear. In this regard, we have shown that TRH elicits a prolonged inhibitory effect on K⁺ stimulated glutamate and aspartate release in superfused hippocampal slices. We have also found that TRH enhances cell survival when added to pituitary adenoma cells (GH-3), neuronal pheochromocytoma cells (PC12) and cultured fetal (F18) hippocampal neurons before, during, or after prolonged toxic glutamate exposure. These data suggest that TRH can produce its neuroprotective effects both pre- and post-synaptically. Interestingly, prolonged exposure of superfused dentate gyrus slices to TRH results in a significant decrease in Galpha_{q/11} levels. Since Group I metabotropic glutamate receptors share the same signal transduction cascade in dentate gyrus granule cells, we suggest that the anticonvulsant role of TRH, in part, involves heterologous receptor downregulation of mGluR_{1,5} glutamate receptors. Clinically, TRH has shown efficacy in the treatment of drug-resistant epilepsies including infantile spasms and Lennox-Gastaut syndrome. Nevertheless, its sustained bioavailability is severely limited because of rapid metabolism and poor penetration through the blood brain barrier. Thus, we fabricated TRH as sustained-release surface-eroding polyanhydride microdisks and observed that this biodegradable complex could attenuate kindled epileptogenesis, indicating that it was delivered to sites where it modulated local excitability. Also, intranasal delivery of unprotected TRH has been shown to inhibit chemically kindled seizures. We suggest that intranasal application of biodegradable surface-eroding TRH-nanostructures would enhance: 1) olfactory nerve uptake; 2) neuronal & transneuronal transport and 3) site-specific bioavailability. Advantages of this therapeutic approach include: 1) ease of use; 2) long term compliance; 3) uninterrupted delivery; 4) ease of dosing and 5) ease of interrupting therapy.

NAP INFLUENCES IMMUNE-MEDIATED RESPONSES: IMPLICATIONS FOR AUTOIMMUNE DISEASES

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Among the known neuroprotective peptides, vasoactive intestinal peptide (VIP) has been linked to neuronal survival and immunomodulation [1,2]. Activity-dependent neurotrophic factor (ADNF) produced by VIP-stimulated astroglia prevents neuronal cell death at femtomolar concentrations [1,3]. The ADNF-like active peptide (NAP) constitutes a part of a new cloned protein namely activity-dependent neuroprotective protein, ADNP [4,5]. NAP has been shown to exhibit potent neuronal protection resulting in enhanced motor, sensory, and cognitive functions [1,4-7]. Here, we reveal that NAP has potent anti-inflammatory properties and immunosuppressive effects on T lymphocytes assayed by proliferation and cytokine responses. Interestingly, NAP inhibits autoantigen-specific T cell responses in an encephalitogenic, autoreactive T cell line (BP10). Experimental autoimmune encephalomyelitis (EAE) was used as an animal model of human multiple sclerosis. Adoptive EAE was transferred by ip injection of activated BP10 T cells. *Ex vivo* treatment of BP10 cells with NAP reduces the onset and severity of EAE. Our finding that NAP is involved in immune regulation indicates that this molecule may have a far more complex role that has been previously anticipated.

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Session 6: Virus modulation of peptide function

SUSTAINED, 6 MONTH ANTIVIRAL BENEFITS IN HIV PATIENTS RECEIVING PEPTIDE T: FLUSHING OF THE CELLULAR RESERVOIRS AND REDUCTION OF PLASMA VIRAL LOAD*

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Persistently HIV infected monocyte/macrophages and derivative brain microglia comprise difficult to treat reservoirs that contribute greatly to NeuroAIDS and are the main impediment to a durable treatment or cure. Current HAART therapies do not control monocyte infection and infected T cells remain, sources of continual reinfection in the body. Therapies, especially non-toxic ones, which address these current therapeutic limitations are needed and hold promise to achieve new benchmarks in patient antiviral treatment. We have therefore studied the CCR5 entry inhibitor DAPTA (Dala1-peptide T-amide) for antiviral effect by analyzing stored plasma, serum, and CSF samples from the randomized double-blind placebo-controlled trial of peptide T for HIV-associated cognitive impairment conducted in the mid-1990's (Heseltine et al., Arch Neurol. 1998 55(1): 41-51.) PCR (Roche Amplicor) analysis of plasma (16 placebo, 17 DAPTA) found a significant reduction (0.54 log₁₀, p=.037) change in viral load between baseline and month 6. Analyses of CSF (44 placebo, 48 DAPTA) found that the placebo group showed slight increase (.06 log₁₀), while the DAPTA showed a slight decrease (-.024 log₁₀), ns. A 6 month open-label study of eleven long-term infected (mean=17 years) patients with stable persistent plasma HIV RNA examined cellular and plasma viral burden. Low plasma viral load did not change in this stable non-progressor cohort, and infectious virus could not be isolated from their plasma suggesting it was devoid of replicative capacity. Cellular infectious viremia was however detected and progressively less virus could be isolated from white blood cells (PBMC's) with DAPTA. All patients which were positive for virus isolation by co-culture at baseline (6/11) became co-culture negative by 24 weeks. DAPTA also flushed the persistently infected blood monocyte reservoir to undetectable viral levels in most patients. Integrated HIV in total PBMCs became undetectable after 44 weeks in one patient we have followed. Five of eleven had a mean CD4 increase of 33%. Immune benefits also included a four-fold increase in gamma-interferon-secreting T-cells (antiviral cytotoxic T cells) which peaked at 8-12 weeks and preceded viral declines suggesting viral clearance may be immune mediated. Peptide T therefore can be shown to have antiviral effects on both cellular and plasma viremia, with no toxicities, and these effects were apparent at 6 months indicating that viral resistance to therapy was not apparent.

Poster Abstract**VASOPRESSIN AND CIRCADIAN RHYTHMS IN SUGAR ADDICTION**

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Addiction is commonly associated with drugs of abuse such as heroin and cocaine. Studies have shown that there is a significant increase in central nervous system dopaminergic activity following addictive drug administration. Additionally, these drugs induce dopamine receptor sensitization and upregulation in the mesolimbic pathway, which projects to the nucleus accumbens in the striatal forebrain, producing pleasurable sensations. Thus, these structures are commonly referred to as the “reward” centers in the brain. Drug addiction has physical effects on the nucleus accumbens and likely explains chemical dependency behaviors in addiction and withdrawal. Recent studies have shown that sugar has the capability to stimulate and increase dopaminergic activity in the nucleus accumbens. Furthermore, excessive sugar intake sensitizes dopamine receptors in a manner identical to other drugs of abuse. Vasopressin is a nonapeptide hormone and neurotransmitter. Studies in our laboratory utilizing vasopressin-containing and vasopressin-deficient rats have shown that vasopressin has an influence on glucose homeostasis. Due to this metabolic phenomenon, vasopressin-deficient rats may have differing responses to the addictive qualities of sugar. The purpose of this study was to investigate the effect of sugar addiction on the circadian rhythms of body temperature and activity of vasopressin-deficient rats. In addition, metabolic effects of sugar addiction, reflected in body weight, food intake, water intake, and blood glucose levels were examined. Twelve vasopressin-deficient animals were implanted with a biotelemetry transmitter and maintained on a 12 hour/12 hour light/dark cycle for four weeks. Throughout this time, subjects were given access to food for 12 hours during the dark period and to water ad-libitum. During weeks two and four, half of the subjects were provided access to a 25% glucose solution for 12 hours in the dark period. During glucose trials, body temperature and activity markedly increased for the experimental group compared to control animals. These animals showed typical physiological and behavioral patterns of addiction, withdrawal, and relapse, comparable to drugs of abuse.

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