University of California, Los Angeles

Theme: A coordinated study of stress, pain, emotion, and sexual factors underlying the pelvic visceral disorders of irritable bowel disorder and interstitial cystitis

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Abstract

The UCLA Center for Neurovisceral Sciences & Women's Health (CNS/WH) is composed of a cohesive group of physician scientists, psychologists, basic scientists and support staff who study interactions between the nervous system and pelvic viscera, with particular emphasis on the interface between stress, pain and emotions, and sex-related differences in these interactions. A lean and well-run Administrative Core has been an essential ingredient in the success of the Center during the past four years and a continuation of this Core is proposed. Primary components of the Administrative Core include the Center Director, Dr. Mayer (who also is Administrative Core Director and PI), Center Co- Director, Dr. Tache (Co-Pi) as well as the Executive Committee made up of the Directors; Project PIs and Core Directors of the Center. An experienced administrator, Sharon Monroe, manages the Directors Office and Administrative Core and the staff is efficient and stable. This leadership team under the Direction of Dr. Mayer directs the major components of the Center operation: managerial, financial, facilitator/, educational, and human information technology. The Center maintains an active External Advisory Board made up of internationally recognized thought leaders in the field of neurovisceral interactions and they provide input into scientific and administrative aspects of Center operations. The UCLA SCOR (the CNS/WH) will continue to be placed organizationally under the umbrella of the Department of Medicine. Through this structure, the SCOR is able to maximize its visibility and its potential for interaction with relevant departments, programs, institutes and centers at UCLA.

Project 1: Differences in Central Stress Circuit Responsiveness Between Women with and without Chronic Pelvic Visceral Symptoms (IBS, IC) and in an Animal Model o Chronic Stress.
Type: Basic

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Abstract

Results generated by the SCOR during the current funding period suggest that key components of central stress circuits are differentially responsive in men and women, and in women with and without irritable bowel syndrome (IBS), leading to sex-differences in peripheral outputs (in the form of the sympathetic nervous system [SNS] and the hypothalamic-pituitary adrenal [HPA] axis), as well as to sex differences in the balance of endogenous pain modulation systems. We propose translational studies to test the primary hypothesis that healthy women are able to attenuate responses of limbic circuits to emotional and disease-relevant psychological stressors, while female patients with IBS (with and without interstitial cystitis [1C] symptoms) have a compromised ability to do so, resulting in greater pain and emotional responses. We further hypothesize that these responses are in part modulated by attenuating effects of estrogen on the central stress system. In this Project we will test the hypothesis of sex-related differences in central stress system activation in human subjects and in an animal model. In Aim 1 we will use a combination of threat-potentiated startle and measurement of a nociceptive reflex to study sex differences in IBS/IC responses of the amygdala and descending pain mechanisms during affective manipulations of threat and emotional picture viewing. In Aim 2, we will use functional magnetic resonance imaging (fMRI) to characterize altered corticolimbic (and especially cortico-amygdala) interactions. In both Aims 1 and 2, we will study both ovulating (follicular, luteal phase) and non-ovulating women and will correlate all responses with plasma estradiol (E2) levels at the time of study. In Aim 3, we will apply a novel brain imaging technique to study sex-related alterations in central stress system activation in a rodent model with face and construct validity for IBS, assessing the central response to a conditioned fear stimulus, and evaluate the role of sex and estrogen in these responses.

Project 2: Sex Differences in Mucosal Neuro-endocrine-immune interactions in IBS Patients
Type: Clinical

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Abstract

This proposal builds on research results obtained during the current funding period of the SCOR which have demonstrated that irritable bowel syndrome (IBS) patients show evidence of enhanced stress responsiveness manifested as dysregulations in the three main components of the central stress response, the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system and the endogenous pain modulation systems. We also found sex differences in the activation of central stress circuits and in the emotional responses to aversive pelvic stimuli. The current proposal (Project 2) aims to test the related hypotheses in IBS patients that sex-related differences in the central stress response are manifested as changes in the periphery in the form of peripheral mediators of the central stress response (HPA axis and sympathetic nervous system [SNS]), and in modulation of the peripheral stress system (colonic mucosal corticotropin-releasing factor (CRF) and noradrenergic signaling systems. We plan to determine if these peripheral changes correlate with subjective IBS symptoms and health-related quality of life. Our specific aims are: 1) To identify sex differences in the expression of the colonic mucosal CRF signaling system (CRF ligands and CRF1 and 2 receptors), and identify possible mediators of this expression (norepinephrine [NE, cortisol) in healthy subjects and IBS patients, 2) To explore the relationship of the CRF signaling system and T lymphocytes in the colonic mucosa and lamina propria by examining whether these T lymphocytes from IBS patients have altered CRF receptor expression and if it is consistent between men and women and IBS vs. controls, and 3) To explore the possible relationships between mucosal CRF signaling system alterations and central measures of increased stress responsiveness (in collaboration with Project 1), and if these relationships are consistent between men and women and IBS vs. controls. In addition to collaborating with Project 1, this proposal will have close interactions with Project 3 and will parallel studies being performed in Project 4 in which the CRF signaling system is being characterized in animal models of IBS (Project 3) and interstitial cystitis (Project 4).

Project 3: CRF Signaling Pathways in Stress-related Visceral Manifestations
Type: Basic

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Abstract

The objective of project 3 is to establish that components of sex difference in rodent models of stress-related alterations of colonic function and visceral pain involve the modulation of corticotropin-releasing factor (CRF) signaling pathways by estrogens. The specific aims based on our previous findings and preliminary data will focus on specific central nervous system sites (Barrington's nucleus/locus coeruleus [LC], sacral spinal cord) and peripheral tissue (colon) at which such estrogen-CRF signaling interactions drive sex differences in the visceral response to stress. Aim 1 will use an electrophysiological approach to establish that a) the activation of LC neurons by colorectal distension (CRD) is enhanced in female compared with male rats through activation of CRF/CRF1 receptor (CRF1R) signaling pathways using selective CRF1R agonists and antagonists, b) prior stress results in sustained enhanced responsiveness of LC neurons to CRD leading to delayed visceral hypersensitivity, and c) selective estrogen receptor (ER) alpha and ER beta agonists exert differential actions on LC neurons responsive to CRD in ovariectomized rats. Aim 2 will use a rat model of allostatic load induced by early maternal separation to characterize sex differences in visceral pain, colonic secretomotor function and CRF signaling pathway responses to an additional chronic psychological stress. Functional studies will be achieved by monitoring abdominal contractions to CRD, changes in colonic permeability and mucus, propulsive motility in male and female rats intact or ovariectomized with replacement by selective ER alpha and ER beta agonists. Laser capture microdissection of colon and sacral spinal cord, RT-PCR for CRF ligands and receptors and immunohistochemistry will be used to assess changes in CRF signaling. Aim 3 will use a genetic model of chronically stressed CRF overexpressing (CRFOE) mice in which we demonstrated an enhanced colonic and bladder voiding to a mild stress in females to characterize a) sex differences in pelvic visceromotor response to stress and CRD, and b) the stress initiating role of CRF1R activation and normalizing action of CRF2R. The proposed studies will help unravel the pathways and molecules involved in the sex differences of visceral response to stress. These findings will provide new insight on mechanisms of irritable bowel syndrome (IBS) where sex differences, association between hypervigilance/anxiety, altered colonic function and visceral pain responses are reported.

Project 4: Role of the Peripheral CRF Signaling System

Type: Basic

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Abstract

Our previous findings have revealed that bladder urothelial (UT) cells exhibit specialized sensory and signaling properties that allow them to respond to their chemical and physical environments and to engage in reciprocal communication with neighboring UT cells as well as nerves in the bladder wall. Interstitial cystitis (1C) is a clinical syndrome that exhibits chronic sensory symptoms in humans such as urinary urgency, frequency and pain. Clinical reports have shown that 1C as well as irritable bowel syndrome (IBS) are comorbid with stress-related events. The experiments proposed in this application will extend new concepts and explore the effects of stimuli including neuropeptide corticotropin-releasing factor (CRF) in UT cells isolated from both normal cats and cats diagnosed with 1C (feline interstitial cystitis, FIC). Because of recent evidence demonstrating a cross sensitization of colon and the bladder we will also examine whether inflammation of the colon may lead to changes in the properties of bladder urothelium. Using a multidisciplinary approach involving transmitter release and novel imaging techniques our goals are to understand how UT cells receive and integrate multiple stimuli including the modulation by stress peptides such as CRF, thus providing an important "link" in the transfer of information from the bladder to the nervous system. Specific Aim 1 will evaluate the expression and origin of the CRF signaling system in FIC, acute cystitis and in CRF-overexpressing mice. Specific Aim 2 will evaluate the effect of CRF on urothelial function. Because of the close proximity of bladder nerves (efferent and afferent) to UT cells, it is likely that pain originating in the colon could ultimately lead to changes in urothelial function. Thus, we will also examine the effect of colon pathology on bladder CRF signaling. Specific Aim 3 will evaluate the involvement of CRF on UT cell communication. Recent evidence has shown that various stimuli elicit Ca2+ waves that propagate through the urothelium. We will use intact bladder and colon sheets and optical imaging in order to study cell-cell communication. Understanding the mechanisms contributing to and maintaining this information transfer may provide important insight for the identification of novel targets for the future clinical management of dysfunctions in pelvic viscera.

CORES

Core A: Administrative Core

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Center during the past four years and a continuation of this Core is proposed. Primary components of the Administrative Core include the Center Director, Dr. Mayer (who also is Administrative Core Director and PI), Center Co- Director, Dr. Tache (Co-Pi) as well as the Executive Committee made up of the Directors; Project PIs and Core Directors of the Center. An experienced administrator, Sharon Monroe, manages the Directors Office and Administrative Core and the staff is efficient and stable. This leadership team under the Direction of Dr. Mayer directs the major components of the Center operation: managerial, financial, facilitator/, educational, and human information technology. The Center maintains an active External Advisory Board made up of internationally recognized thought leaders in the field of neurovisceral interactions and they provide input into scientific and administrative aspects of Center operations. The UCLA SCOR (the CNS/WH) will continue to be placed organizationally under the umbrella of the Department of Medicine. Through this structure, the SCOR is able to maximize its visibility and its potential for interaction with relevant departments, programs, institutes and centers at UCLA.

Core B: Neuroendocrine Assay Core

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Abstract

The Neuroendocrine Assay Core will provide the UCLA Center for Neurovisceral Sciences and Women's Health with state of the art resources and expertise related to the measurement of neuroendocrine mediators involved in central and peripheral stress signaling pathways. Additional services related to measurements of the CRF signaling system components have been added to accommodate changes in the needs of the projects in renewal application and personnel have been changed to reflect these requirements. The Neuroendocrine Assay Core will be directed by Dr. Gordon Ohning, MD, PhD and co-directed by Dr. Yvette Tache, Ph.D and will be an independent Core lab within the next funding period. The Core will utilize equipment and resources that were acquired during the first funding period or that are currently available within existing laboratories. Dr. Ohning has training in Internal Medicine, Gastroenterology and the Postdoctoral Research Training Program in Psychiatry and Biobehavioral Sciences. He has considerable experience in radioimmunoassay, immunohistochemistry and enzyme immunoassay methods. Dr. Tache has extensive experience in brain-gut mechanisms and CRF receptor signaling pathways and will provide the necessary expertise for the added Core services related to the gene expression analysis for rat and human CRF-like receptors and ligand systems. Drs. S. Vincent Wu, Ph.D. and Pu-Qing Yuan, Ph.D. both have considerable experience in molecular biological techniques, including the design and production of molecular probes, the isolation, purification, and identification of DNA, RNA and proteins expressed by cell culture and from tissue extraction, and in the techniques of RT-PCR, real-time quantitative PCR, and western blot analysis. Honghui Liang will be the primary technician responsible for the assisting in the assays within the scope of the Core services and will coordinate efforts with Center Investigators utilizing the Core Services and quality control of all procedures. The Core personnel will work together as a team to provide a cohesive and efficient Core that will not only provide analysis of serum, salivary, tissue samples from both human biopsies and animal tissues, but also provide consultation on the correct methods for processing samples and interpreting results. The Core Laboratory will also provide training as part of the Career Development Program, and participate at all levels in Center operations.

Core C: Neuroimaging Core

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The joint SCOR/R24 Neuroimaging Core is a state of the art facility which will provide the UCLA SCOR with resources dedicated to biomedical imaging and analysis of the central stress, pain, and emotional systems. This entity will be an expansion of an existing Neuroimaging Core of the UCLA Center for Neurovisceral Sciences & Women's Health (CNS/WH) that has been initiated with core funding from a NIH R24 mind body center infrastructure grant in 2003 to study brain mechanisms underlying the interface of stress, pain and emotion with a special emphasis on sex-related differences. As such, the proposed joint SCOR Neuroimaging Core will utilize the considerable expertise, equipment and other resources that have been acquired to fulfill the goals of the R24 Neuroimaging Core. The SCOR portion of the Core will only be available for SCOR projects of the UCLA SCOR and for the planned collaborative efforts with two other SCORs (Yale, U. Maryland) should they be funded. This joint Core will be directed by Dr. Emeran Mayer MD (who is the director of the existing Core), and co-directed by Dr. Bruce Naliboff, Ph.D. Dr. Mayer is a Professor of Medicine, Physiology, and Psychiatry with a long-standing research interest in brain-gut interactions. Dr. Mayer will be responsible for all Core functions, allocation of resources to facilitate, and optimize all SCOR-related research projects and collaborations. Dr. Naliboff is a Clinical Professor in the Dept. of Psychiatry & Biobehavioral Sciences at the David Geffen School of Medicine at UCLA, Director of the CNS/WH Psychophysiology and Pain Assessment Core. He has considerable expertise in stress psychophysiology as well as brain imaging techniques in the study of visceral pain, autonomic correlates, and connectivity modeling. Dr. Naliboff will supervise all aspects of data collection related to pain and autonomic response assessment in Projects 1 and 2 and in the planned inter-SCOR collaborations. A team of other researchers and technicians has been recruited for the development, acquisition, and analysis of brain imaging data to fulfill the scientific aims of the existing Core. These same personnel will work in concert with the Director and Co-Director to

provide timely access to all SCOR investigators for performing image acquisition, analysis, as well as consultation on the correct methods for obtaining and processing imaging data and the interpretation of results.