Bringing the brain back into medicine

Spring 2013

UCLA CNS

Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress

David Geffen School of Medicine at UCLA

From the Desk of Emeran A. Mayer, MD
Center Director

The overall mission of the UCLA Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress is to promote research and clinical applications on the role of the brain in health and disease.

Several Center Programs have initiated highly innovative research projects into mechanisms by which the mind, brain and body interact. These projects address a wide range of topics, ranging from the neurobiological basis of resilience to how meditation can improve symptoms of chronic abdominal pain to how the brain can influence the heart in the context of life threatening arrhythmias. Finally, Center investigators are playing a pioneering role in studying how the bacteria in our intestinal tract ("gut microbiota") can influence brain function and how this influence may play a role in a wide range of disorders. Results from these studies will have significant implications for more effective treatments for chronic stress-related disorders.

In this edition of the Center newsletter, we are highlighting a few of these areas of active investigation. These accomplishments have been achieved despite significant reductions in federal support for research and the concern that this situation is likely to get worse in the next year or two. We would like to thank all of you who have generously supported the Center during these difficult times and have allowed it to continue its groundbreaking research.

Samueli Institute Workshop, "Towards a Systems Model of Resilience" - Irvine, CA (Page 4)

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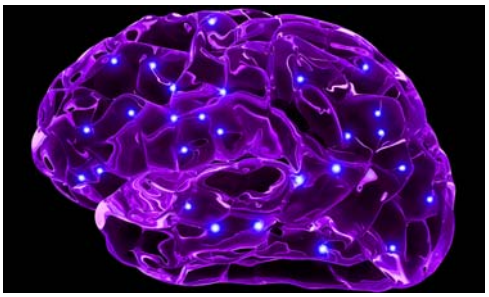
Linzess

A new medication, Linzess® (linaclotide) was recently approved by the Food and Drug Administration (FDA) for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC). Linzess has been shown in clinical trials to be effective in relieving abdominal pain and constipation.

Center investigators conducted one of the original experimental studies which showed that linaclotide decreased sensitivity of the bowels. Subsequent clinical trials have demonstrated this medication's effectiveness in reducing abdominal pain. Dr. Lin Chang is currently conducting another study at our Center to determine the reasons why patients with IBS-C and CIC may respond to Linzess at the level of the colon mucosa (lining of the large intestine).

Gut Feelings Revisited: How Bacteria in Our Intestinal Tract Communicate with the Brain

The last few years have seen remarkable discoveries about how the microorganisms in our gastrointestinal tract (the so-called "gut microbiome" or "gut microbiota") can communicate with the brain. What just 5 years ago sounded like science fiction has now become a major research area in gastroenterology and neuroscience. This topic of gut-microbiome-to-brain signaling is the major focus of a recent publication by Center investigators in the prestigious journal, *Gastroenterology*.



"Our bodies are made up of 10 times as many bacterial cells (100 trillion!) as human cells and the number of bacterial genes is 100 times greater than human genes."

The facts are startling: Our bodies are made up of 10 times as many bacterial cells (100 trillion!) as human cells and the number of bacterial genes is 100 times greater than human genes. This means only 10% of all the cells making up our bodies are human cells! Rather than just playing a role in breaking down indigestible parts of our diet (fiber), we now know that there is extensive bi-directional communication between these cells and the cells in our digestive tract, and signals from these bacteria can reach as far as our immune system, the liver and the brain. Studies in animals have shown that gut microbiota can affect emotional behavior, pain and stress sensitivity and the development of signaling systems within the brain.

In a recently published study by Center investigators, lead author Dr. Kirsten Tillisch, for the first time, has shown that such gut-microbiota-to-brain signaling can also occur in healthy people. Young, healthy females underwent functional brain imaging (fMRI) before and after a 4-week course of a mix of probiotic organisms contained in a commercially available yogurt. Their brain responses were compared to 2 control groups, one who received a product of identical taste but not containing probiotics, the other group not receiving any product. Remarkably, the subjects who had ingested the probiotic mix showed dampened responses in a network of brain regions involved in sensory perception and affective responses.

Future studies are planned to better characterize these interactions between the universe of our gut microbiota and our brain and to address some intriguing questions: Do unique patterns and composition of our intestinal microbiota correspond to differences in brain structure and function? What role do our microbiota play in the way we feel? And is it possible that alterations in our gut microbiota play a role in a range of chronic brain diseases such as autism, Alzheimer's disease and Parkinson's disease?

Using Body and Mind to Treat Post-Traumatic Headaches

Over the past year, CNS investigators under the leadership of Drs. Bruce Naliboff and Kirsten Tillisch, and with the generous support of the Gerald H. Oppenheimer Family Foundation, have begun new initiatives in Mind-Body research and interventions targeting problems of our returning Veterans. Drs. Naliboff, David Shapiro and Leila Shahabi of the CNS in collaboration with Dr. Milena Zirovich at the VA Greater Los Angeles Healthcare System (VA-GLAHS) have initiated a new study of Iyengar Yoga training for Veterans with headaches with and without Post-Traumatic Stress Disorder (PTSD). Yoga interventions have shown success with several chronic pain problems, but this study will be the first trial of a Yoga training program specifically designed for Veterans with headaches. The program will teach Yoga exercises in a series of classes and provide DVDs for home practice.

The Brain Science of Meditation

Investigators at the Center, under the leadership of Dr. Tillisch, are beginning a groundbreaking clinical trial to study the neurobiological mechanisms and beneficial effects of Mindfulness-Based Stress Reduction (MBSR) on chronic symptoms of abdominal pain and discomfort in patients with irritable bowel syndrome (IBS). MBSR utilizes weekly group practice, education and daily home practice designed to be efficient and practical for our current lifestyles.

Funded by a grant from the National Center for Alternative and Complementary Medicine (NCCAM), Drs. Tillisch and Naliboff will examine the structure and function of the brain before and after MBSR using advanced multimodal neuroimaging techniques. At the same time they will study the effect of MBSR on the peripheral nervous system, on signs of inflammation in the blood and on the composition of bacteria in the gut (gut microbiome). By gaining a clearer understanding of the mechanisms underlying the beneficial effects of MBSR in IBS, we hope to develop even simpler and more accessible Mind-Body treatments for patients with stress-related medical problems.

It is expected that both the Yoga and Mindfulness projects will provide valuable initial data to guide new collaborative grant submittals and clinical programs at the VA-GLAHS. The leadership of the CNS and the VA-GLAHS have met several times in the past year and fully expect further exciting collaborative projects to emerge in the coming months.

UCLA Digestive Health and Nutrition Clinic

The UCLA Digestive Health and Nutrition Clinic, under the direction of Dr. Lin Chang, Co-Director of the Center, opened in August 2012 and treats patients with digestive disorders including irritable bowel syndrome, celiac disease, chronic constipation and diarrhea and cyclical vomiting syndrome.

The program offers state-of-the-art diagnostic evaluation, including detailed assessment of Mind-Body imbalances, stress history and integrative medicine treatment. If indicated, comprehensive dietary evaluations and management plans will be provided and clinic physicians will work closely with integrative medicine providers in the community. This clinic is at the forefront of new, innovative developments in this field of medicine and gives patients a much needed single place where they can receive care.

To make an appointment, please call (310) 206-6279.

Modulating Brain-Heart Connections to Treat Abnormal Heart Rhythms

Interrupting the nerves connecting the brain and spinal cord with the heart is sometimes used to treat severe cardiac arrhythmias resistant to conventional therapies. The most common sites targeted are critical bundles of nerve cells that control heart function, the Stellate Ganglia. This procedure, known as cardiac sympathetic denervation, has been used by Dr. Kalyanam Shivkumar and his colleagues, Drs. Aman Mahajan, Marmar Vaseghi and Olujimi Ajijola, in patients lacking further treatment options. In collaboration with Drs. Naliboff and Shahabi, a novel research program has been initiated to identify neurophysiologic biomarkers of response to cardiac sympathetic denervation in order to better gauge its effects on individual patients and help identify good candidates for the procedures. These studies involve sophisticated non-invasive measures of nerve and cardiac function, along with clinical symptoms. Studies of this kind have not been previously used in this situation.

The Neurocardiology Program within the Center has also been spearheading efforts to understand the precise effects of nerve signals delivered from the Stellate Ganglia to the heart. In the first human study of its kind, the neurocardiology group and other colleagues at the UCLA Cardiac Arrhythmia Center, have performed in-human stimulation of the Stellate Ganglia, quantifying its effects on human cardiac electrical activity. The data collected will lead to better clinical care and new research on brain-heart interactions in cardiac diseases. This work is supported by a recent grant from the National Institutes of Health (NIH), providing almost $2 million of research funding support to investigate brain-heart connections in cardiac electrical diseases.

The Emerging Biology of Resilience

While biomedical research has traditionally focused on disease mechanisms, there has recently been growing interest in the biological mechanisms underlying our ability to bounce back from stress, infections or injury. This interest in the biology of resilience has been triggered in part by the military's desire to decrease deployment-related morbidity by increasing resilience of the armed forces, and in part by the changes in the healthcare system which aims to keep people in optimal health, thereby minimizing healthcare utilization.

On January 22-23, 2013 an interdisciplinary workshop on resilience ("Towards a Systems Model of Resilience") was organized by the Samueli Institute, a non-profit organization fostering the scientific exploration and implementation of healing processes. The workshop was attended by an international group of experts from many disciplines (neurobiology of stress, neuroscience, systems biology, medicine, psychology and public health) and by high-ranking military officers. Dr. Mayer presented results from recent CNS brain imaging studies which showed that subjective measures of the resilience in healthy people are reflected in the connectivity of distinct brain networks. The CNS plans to continue these studies with the goal of identifying brain "signatures" of subjects with high and low resilience. Such markers may become clinically relevant in the future to identify a person's risk level to develop a variety of chronic diseases under stressful conditions. People with ineffective resilience mechanisms may benefit from various Mind-Brain-Body interventions such as meditation or cognitive behavioral therapy.