Bringing the brain back into medicine

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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

In this edition, we are once again highlighting exciting news from the Programs of the Oppenheimer Center. Each of these Programs addresses a different aspect of brain-gut interactions and how these interactions may be altered in different diseases. Three such aspects are: Obesity, chronic pain and autism. For details about the Oppenheimer Center and its individual Programs, please visit uclacns.org.

We would also like to thank the small group of individuals who have continued to generously support our research portfolio. While all the Programs have been highly successful in competing for federal funding, philanthropic support remains essential to support junior researchers and to start high risk pilot-high yield projects which may lead to federally funded grants. Such projects include the development of the web-based pain treatment program discussed in this issue, research into how dietary changes can affect the gut microbiome and the mind, and research into finding new obesity treatments aimed at the brain gut axis.

New CNS Ingestive Behavior and Obesity Program

Obesity is a world pandemic and America is the epicenter. It seems simple enough, people become overweight when calories consumed exceed expended. Nutritionists have known this for 200 years, and yet, no diet has solved the problem. The problem has actually worsened. Thus, the question driving our research is: why do overweight people continue obesogenic behaviors even though they deconstruct their lives on multiple levels?

At the CNS Ingestive Behavior and Obesity Program, we diligently work to answer vital questions in key areas:

1) Are there structural and functional differences in key brain regions of obese individuals that control eating behavior and the hedonic value of eating? And If so, can we use that information to treat/prevent obesity?
2) Does obesity affect palatable (rich calorie dense) food preferences?

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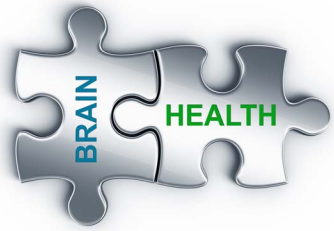

New CNS Ingestive Behavior and Obesity Program

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3) Do compulsive overeaters experience decreased taste sensitivity?
4) Do race, sex and cultural stressors influence ingestive behaviors?
5) Does the gut microbiome affect eating behavior in obesity and in weight loss?

Why should we care about obesity? Aside from the more than $200 billion dollars that it costs, in 2008, according the World Health Organization more than 1.4 billion adults were overweight. Of these over 500 million were obese. We are a social species. The question is not why should we care about obesity. The question is how could we not care.

How is obesity related to brain function? In theory, your brain's job is to oversee your global wellness which includes homeostatic maintenance, or making sure to consume the correct amount of calories to meet bodily needs. Yet, 1.4 billion people are overweight. Are all of those brains broken? Perhaps it is genetic. Overweight children generally have overweight parents, or at least that is how it appears from casual observation. There is always a genetic component to all things human, but genetics is not the issue here, per se.

Neuroimaging advances have provided unique insight into how the brain processes external food cues and constructs flavor in creating the hedonic value of eating that cause dopamine release in the brain's reward circuitry. Researchers have observed differences in overweight populations, compared to normal people in dopaminergic response to food cues. However, one must remember that the brain uses dopamine to motivate humans to participate in life promoting behaviors. Thus, dopamine releases on the anticipation of the reward of eating, not the actual eating itself. Studies have also shown that the area of the brain that releases dopamine from the actual hedonic pleasure of eating decreases in compulsive overeaters compared to normal eaters. How tragically ironic that is. It seems overeaters eat more, but enjoy their food less.

What kind of obesity research is being done at the Ingestive Behaviors and Obesity Program? Our group is interested in several topics related to obesity. For example we are studying the mechanisms by which weight loss surgery (gastric bypass, gastric sleeve) can help people to lose weight. We know from several studies that surgically reducing the size of the stomach is not the main mechanism for weight loss. Surprisingly, several studies have demonstrated that weight loss surgery produces changes in food preferences and appetite. Our research aims to find out what causes these unexpected changes and if they play a major role in weight loss. To answer these questions, we study brain activity and structure in obese women before and after bariatric surgery to determine how brain changes associated with the surgery are related to weight loss, appetite reduction and changes in food preferences. The long-term goal is to find a non-invasive treatment capable of reproducing these brain changes and associated reductions in appetite without surgical intervention.

In addition, we are interested in how obesity changes the structure and connections between different parts of the brain. This research hopes to find possible areas of the brain involved in the development of obesity that we could target in the future with therapies to prevent or reduce obesity. Concomitantly, we have begun collaborating with pediatricians at UCLA to study how food preferences and eating habits are related to obesity in children and how a structured program with emphasis on food choices and physical activity influences brain activity and eating behavior.

A common research theme in adults and children is trying to understand the underlying mechanisms that cause and sustain obesity, and how those mechanisms can help guide the development of new therapies that are adaptable to individual differences in patient responses to those interventions. To learn more, visit uclacns.org/programs/ingestive-behavior-and-obesity-program.

New Help for Patients Coping with Chronic Pain

The CNS Pain Research Program is moving ahead on an ambitious project to use internet technology to help patients with chronic pain including those with Irritable Bowel Syndrome, Inflammatory Bowel Disorders, and Heart Arrhythmias. It is well recognized by both patients and providers that strategies for decreasing illness related stress and anxiety, improving sleep, and improving pain coping can be extremely helpful as additions to standard medical treatments. Unfortunately for the majority of patients these interventions, provided individually by specially trained psychologists or other mental health clinicians, are not realistically available due to distances, expense and shortage of trained providers. The good news is that clinicians including several from CNS are developing technology assisted programs that will enable patients to connect with an expert provider, learn new skills and receive feedback and support all from their own home computer or other internet device

Building a patient-centered system. How would this system work? The last few years has seen a growing interest in using the internet to assist health care delivery, including delivery of psychological and educational services, primarily for mental health problems. These programs range from fully automated self-guided educational programs to real time therapy sessions via internet video conferencing. At the CNS we believe there is great potential in these new technologies but are also aware that key elements of compassionate and patient centered care need to be preserved when using technology in order to keep patients involved, motivated and active in their own treatment. We also want to make sure that we promote strategies that are proven in empirical studies to be effective for symptom improvement and increasing well being and not just those that are easy to put up on the web. Our Technology Assisted Well Being program for pain is based on three essential principles.

- Integration of the well being program with medical care as opposed to being a 'stand-alone' separate endeavor.
- Maintaining a personal relationship with a trained provider within the system to provide electronic feedback, motivation and support.
- Inclusion of both generic and patient problem-specific elements so the intervention addresses patients' specific problems in the context of overall pain management strategies.

Our program content is based on Cognitive Behavioral Therapy, the most successful and empirically validated of the self-management approaches in chronic pain and illness related anxiety. The program is online, interactive and self-paced.

Short and long term goals. We are now working on development and fund-raising for the first demonstration product, targeted to the most common of the visceral pain disorders, Irritable Bowel Syndrome. By design this is a modular program with a significant portion of the content being applicable to most patients coping with a persistent pain or other distressing medical problem and the remainder of the modules being illness or population specific. Therefore once the IBS product is running and tested we will begin to develop other modules in conjunction with the appropriate specialist clinicians. Likely targets may include cardiology (e.g. defibrillator-related anxiety), Inflammatory Bowel Disease and pregnancy-related anxiety. The long term plan is to make this form of patient centered intervention available to all relevant patient groups as part of their UCLA care.

CNS Student Training Program – Featured Student

One of the most rewarding missions of CNS is the training and mentoring of the next generation of doctors and neuroscientists. Currently, the Center is proud to include in its family nearly a dozen students ranging from college undergraduates to post-doctoral scholars.

One of these students is José Castellanos, a second year UCLA undergraduate student majoring in neuroscience. He is the oldest of 3 children born to Mexican immigrant parents and is the first in his family to go to college. While his mother completed high school in Mexico, his father ended his formal education at the 5th grade. Both of his parents work in the farmlands of McFarland in San Joaquin Valley, in the same fields where Cesar Chavez once worked.

Watching his parents toil in the fields as he was growing up, he knew he wanted a better life for himself and for his family and that one of the keys to achieving that goal is the attainment of higher education. He also grew up in an alcoholic home. His father's alcoholism had a devastating effect on his entire family, including the divorce of his parents. The profound effect this disease had on his life is what sparked his interest in learning how the human brain works and his motivation for finding a way to cure alcoholism and other addictions. He is fascinated by the fact that the "brain has the capacity to study itself, a super complex computer that can analyze itself" and has the ability to heal itself.

In addition to his studies, José finds time to volunteer with the Central Valley Project UCLA, a student group whose goal is to inspire youths in the Central Valley, an area that is rife with gang and drug activity, to reach their full potential through higher education just as he is doing.

How Gut Microbes and the Brain Communicate – A Clue to the Pathophysiology of Autism?

The concept that altered communications between the gut microbiome and the brain may play an important role in human brain disorders has recently received considerable attention. This new way of conceptualizing brain disorders such as Alzheimer's disease, Parkinson's disease and autism spectrum disorder (ASD) as being related to altered influences from the gut is the result of provocative preclinical studies in animal models. Some clinical evidence generated by investigators at CNS also support these early hypotheses about such communication in health and disease.

Gastrointestinal symptoms are a common comorbidity in patients with ASD, even though the underlying mechanisms are largely unknown. In addition, alteration in the composition of the gut microbiome and in the metabolic products that these microbes generate have long been implicated as a possible causative mechanism contributing to ASD pathophysiology. This hypothesis has been supported by several recently published evidence from rodent models of autism induced by prenatal insults to the mother. In rodent models, such insults include maternal infections and exposure to certain drugs, such as the anti seizure drug valproic acid. Recent evidence in one such model involving maternal infection is characterized by alterations in behavior, gut physiology, microbial composition and related metabolite profile. Intriguingly, some of the observed abnormal behaviors could be reversed by the administration of a specific probiotic, a microorganism with a beneficial effect on the host. Based on the concept of altered gut microbial metabolites playing a role in the development and clinical course of ASD, fecal microbial transplants are being explored as a potential therapy for some ASD patients. CNS investigators are part of a research proposal submitted by the Arizona State University to the Autism Speaks organization. This proposal aims to investigate the effect of fecal microbial transplants on behavior and brain alterations in ASD children.