$8 million NIH grant will fuel research on obesity, diabetes, heart disease

An $8 million grant from the National Institutes of Health will enable UT Southwestern to investigate how fat tissue "talks" to the brain and the liver to promote inflammation-related disorders such as diabetes, heart disease and obesity.

The five-year grant takes advantage of expertise across the campus, including faculty in the Touchstone Center for Diabetes Research, the division of hypothalamic research, and the departments of molecular genetics, internal medicine, and pharmacology.

"We're excited about tackling the complexity of how adipose [fat] tissue, the brain and the liver talk to each other and how this cross talk affects...

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Hungry for knowledge

Imagining glancing in the mirror after you've just devoured a huge steak, a baked potato loaded with butter, cheese and sour cream, and a piece of cheesecake.

You know that you've probably gained weight and your scale confirms this fact the next morning, but where did the extra weight go and how did you gain it? Those are some of the questions that Dr. Deborah Clegg, assistant professor of internal medicine and clinical nutrition at UT Southwestern, hopes to answer through her research with the Center for Human Nutrition and the Touchstone Center for Diabetes Research.

"If you're a man, you know that when you've overconsumed at the steak restaurant, you loosen your belt a little bit to expand that beer belly or visceral depot. So, your fat cells go directly to that depot," said Dr. Clegg, who took part in a recent panel discussion with Drs. Joel Elmquist and Elizabeth Parks on the relationship between appetite and hormones. "And if you're a woman, you know that your fat goes directly to your hips and thighs.

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"But how does a fat cell know where it’s supposed to go?"

“One of the things we’re trying to do is answer that simple question,” Dr. Clegg said at the Friends of the Center for Human Nutrition fall luncheon.

Drs. Clegg, Elmquist and Parks discussed their research projects and interests and then took questions during the P. O’B. Montgomery Fall Luncheon. Dr. Scott Grundy, director of the Center for Human Nutrition and holder of the Distinguished Chair in Human Nutrition, moderated the panel.

Dr. Clegg said part of the mystery surrounding fat is that once women pass through menopause, their fat starts to accumulate in the visceral depot – just as it does in men. Research has shown that fat deposited in this area is highly correlated with metabolic diseases such as type 2 diabetes.

Another area of interest to her is how fatty acids interact with each other.

“We recently published a study showing that if you eat a high-fat diet for three days in a row, your brain becomes less sensitive to the hormones that tell you that you’ve eaten too much and need to back away from the table,” she said. “We discovered that this happens over a relatively short period of time, and, that by the third night, you can probably eat a lot more calories than you did the first night.”

**Timely findings**

Dr. Elizabeth Parks, associate professor of clinical nutrition and internal medicine at UT Southwestern, focuses her research on developing new ways to study body metabolism. She said the popular conception that a calorie is a calorie is simply not supported by the facts.

“How you process food really depends on the environment that the calorie comes into,” she said.

“When we wake up in the morning and our glucose stores are really low, a carbohydrate, in cereal, for example, is going to fill up your body’s glucose stores so that it can be used later by the brain.

“By lunch, some of our data would suggest that carbohydrates will continue to fill up your glucose stores, some will be burned and some will start to be made into body fat. A carbohydrate that comes in at night, however, goes directly into body fat synthesis.”

She said that the key to weight loss and maintenance may involve shifting food intake patterns to the early morning hours.

“Sixty percent of Americans eat 60 percent of their calories after 6 o’clock at night,” she said. “It is that pattern that we try to change when we work with our patients in our weight-loss study.”

**Brain food**

Unwiring how the brain controls food intake and body weight keeps Dr. Joel Elmquist busy.

Dr. Elmquist, chief of hypothalamic research at UT Southwestern, said that while many people have never heard of the hypothalamus, it is the one part of the brain absolutely required for life.

“It controls all basic life functions including the drive to eat and how you control your body weight,” said Dr. Elmquist, professor of internal medicine and pharmacology. “We’ve set up a center here at UT Southwestern in combination with the Center for Human Nutrition, Touchstone Center for Diabetes Research and the Taskforce for Obesity Research that’s trying to understand how the brain – specifically this section of the brain – controls food intake and body weight.”

Researchers primarily use mouse models to understand how the brain works.

“The reason we use mice as a model is because we can do genetic tricks in mice that we can’t do in any other species,” he said. “The mouse genetics are very valuable to us because they help us to understand the basic principles of how the brain works. As a more translational example, we recently used our mouse models to understand how the drug Fen-phen works.”

“Sixty percent of Americans eat 60 percent of their calories after 6 o’clock at night. It is that pattern that we try to change when we work with our patients in our weight-loss study.”

— Dr. Elizabeth Parks
NIH GRANT

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metabolism and inflammation," said Dr. Philipp Scherer, director of the Touchstone Center and principal investigator of the new project. "Getting this grant validates that the UT Southwestern metabolism group is doing state-of-the-art science."

In 2007, the Taskforce for Obesity Research at UT Southwestern (TORS) received a $22 million NIH grant to enhance the institution's groundbreaking obesity research.

Dr. Scherer, who holds the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research, said that while there is clearly synergy with the TORS grant, this new effort is unique because it is specifically focused on phenomena related to inflammation, considered an underlying cause of metabolic disorders in humans.

"We're especially interested in understanding how the brain and the liver influence inflammation and how inflammation influences metabolism within other organs. Those are just a few of the questions our team plans to tackle," Dr. Scherer said.

Large fat cells are a particular area of focus, he said, because they typically lead to increased cell death and systemic insulin resistance. Under normal circumstances, fat cells continue to grow until the extracellular matrix they've built around themselves is so strong that it's no longer flexible. Once that happens, the cells become inflamed and may contribute to the development of diabetes and heart disease.

"Our research benefits from a multidisciplinary approach and a willingness to share diverse expertise in working toward a common goal," he said. "Models generated for one project are pivotal for the other projects, just as the physiological or molecular expertise of one project leader will be critical to the success of future projects."

The five laboratories involved in the project will work individually on two common areas: identifying the critical sites of action for lipid-related inflammation in the periphery of the body as well as the brain, and identifying the biochemical signals that take place in the body after exposure to high-fat, lipid-rich foods.

Lipids encompass a broad group of naturally occurring molecules, including fats, fatty acids and cholesterol.

Other investigators involved in the program include Dr. Joel Elmqvist, professor of internal medicine, psychiatry and pharmacology, chief of hypothalamic research, and holder of the Maclin Family Professorship in Medical Science, in Honor of Dr. Roy A. Brinkley; Dr. Jay Horton, professor of internal medicine and molecular genetics, and holder of the Dr. Robert C. and Veronica Atkins Chair in Obesity & Diabetes Research; Dr. Deborah Clegg, assistant professor of internal medicine and clinical nutrition; Dr. Joyce Repa, associate professor of physiology and internal medicine; Dr. David Mangelsdorf, chairman of pharmacology and holder of the Distinguished Chair in Pharmacology and the Beatrice and Miguel Elias Distinguished Chair in Biomedical Science; Dr. Laurent Gautron, assistant instructor of internal medicine; Dr. Syann Lee, assistant instructor of internal medicine; and Dr. Makoto Fukuda, instructor of internal medicine. \%

Newsmakers

Dr. Elizabeth Parks

Dr. Elizabeth Parks, associate professor of clinical nutrition at UT Southwestern, has been appointed to the editorial board of Advances in Nutrition, a new online peer-reviewed journal produced by the American Society for Nutrition. The bimonthly journal, which debuted in November, is designed to both explain the significance of new research findings as well as highlight research gaps and future directions in the field of nutrition. Dr. Parks joined the UT Southwestern faculty in October 2005.

Lona Sandon

Lona Sandon, assistant professor of clinical nutrition at UT Southwestern, recently received an Innovation in Practice and Education award from the American Dietetic Association. The association bestowed the award for her "communication and collaboration skills using current technology for enhancing education of dietetics students." She was one of three registered dietitians selected by ADA members to receive the award, which is designed to promote innovations in education and training of clinical nutrition students and practitioners. Ms. Sandon joined the UT Southwestern faculty in July 1997.
A match made in Texas

New lipid and diabetes director found his passion at UT Southwestern. The opportunities that attracted Dr. Frederick Dunn here in the 1970s brought him back in 2005.

Chicago native, Dr. Fredrick Dunn had absolutely no interest in moving to Texas. His first wife, Susan, was even more adamant about her desire to avoid Texas when it came time to complete his internship and residency in internal medicine.

But when the recommendations for UT Southwestern kept piling up, Dr. Dunn hopped on a plane to Dallas. “I was impressed,” said Dr. Dunn, who received his medical degree from the University of Illinois at Chicago.

When Dr. Dunn matched with UT Southwestern, the couple packed up and moved to Texas, where he dove right into the clinical and research opportunities available here.

He worked with faculty members including Dr. David Bilheimer, former professor of internal medicine at UT Southwestern, and Dr. Philip Raskin, professor of internal medicine, director of the University Diabetes Treatment Center at Parkland Memorial Hospital and holder of the Clifton and Betty Robinson Chair in Biomedical Research. Dr. Daniel Foster, professor of internal medicine and holder of the John Denis McGarry, Ph.D., Distinguished Chair in Diabetes and Metabolic Research, was his first attending physician.

“I also collaborated with Dr. Grundy, who was in San Diego at the time,” he said, referring to Dr. Scott Grundy, director of the Center for Human Nutrition and holder of the Distinguished Chair in Human Nutrition. “One of my projects was to set up a method for looking at triglyceride metabolism that Dr. Grundy had developed.”

Dr. Dunn said he considered it a real privilege to study at UT Southwestern in the 1970s.

“We were leading the country in metabolism research,” he said. “We were focused on the role of LDL [low-density lipoprotein, or “bad” cholesterol] and atherosclerosis. I went up to Boston and they weren’t nearly as aggressive. They were still focused on carbohydrate restriction – not cholesterol or fat intake.”

25-YEAR DETOUR

He left UT Southwestern in 1980 and spent the next 25 years honing his research skills at institutions and corporations including the Joslin Diabetes Center, Harvard Medical School, Duke University Medical Center and Merck. He also worked at Tularik, a San Francisco-based bio-tech company.

Dr. Dunn said he enjoyed his career in the pharmaceutical industry, but returned to UT Southwestern because he missed his clinical work.

“Dr. Grundy invited me to join him in the lipid clinic at the VA,” said Dr. Dunn, who now works as director of the Lipid and Diabetes Management Services at the Dallas VA Medical Center.

Besides seeing patients on both an inpatient and outpatient basis, Dr. Dunn oversees a team of people working in the diabetes clinic. Since returning in 2005, he has also overseen the clinic’s expansion from being open half a day each week to five full days and the development of an education program certified by the American Diabetes Association.

“We anticipate that 25 percent of the patients at the VA have diabetes,” he said. “We only see the most complicated cases, but our education program is available to everyone. Many of the materials we use were developed by the Center for Human Nutrition.”

Dr. Dunn also manages the day-to-day operations of the VA’s lipid clinic, which provides outpatient consultation services for the treatment and management of patients with lipid-related disorders.

STILL RESEARCHING

Though his clinic responsibilities keep him busy, Dr. Dunn hasn’t sworn off research. He’s a co-investigator for a number of Center for Human Nutrition research projects under way at the VA Medical Center at Dallas and at the Clinical and Translational Research Center (CTRC) on the UT Southwestern campus.

“One of the projects that I’m working on involves using very concentrated insulin to treat patients who are very insulin-resistant,” he said. “I’m also involved in studies related to the development of new treatments for diabetes as well as a better understanding of the mechanisms that cause some people to develop diabetes and metabolic syndrome.”

More than 36 years after arriving at UT Southwestern as an intern, Dr. Dunn said he’s glad he made that trip to Texas.

“UT Southwestern remains at the forefront of diabetes and nutrition research,” he said. “It was a privilege to study here, and it’s a privilege to again work with such a talented and dedicated group of people.”

Dr. Dunn and his wife, Dr. Priscilla Holland currently reside in Dallas. He has two grown children.
The key to burning off a big meal may be all in your head

A n enzyme in the brain known as PI3 kinase might control the increased generation of body heat that helps burn off excess calories after eating a high-fat meal.

The increase in energy expenditure, called a thermogenic response, burns calories even in the absence of exercise, so understanding how it is regulated could aid efforts to combat obesity, said Dr. Joel Elmquist, professor of internal medicine and pharmacology at UT Southwestern and co-senior author of the mouse study, which appeared in Cell Metabolism.

"We found that the mice with reduced PI3 kinase activity in specific neurons in the brain gained weight because they were unable to produce this thermogenic response," said Dr. Elmquist, adding that the physical activity levels of the mice with reduced PI3 kinase did not change. "These mice were more susceptible to diet-induced obesity."

It's unclear whether the findings are translatable to humans, because one of the tissues that mediates the thermogenic response is brown adipose tissue, a type of fat uncommon in adult humans.

"Brown adipose tissue is found in babies – that's why they're so warm – but it's unclear whether the tissue has the same physiological role in adult humans that it does in rodents," said Dr. Elmquist, who holds the Maclin Family Professorship in Medical Science, in honor of Dr. Roy A. Brinkley. "What is clear, however, is that specific brain cells and PI3 kinase seem to play a key role in how mice, and potentially humans, respond on a physiological level to a high-fat diet."

Dr. Yong Xu, instructor of internal medicine at UT Southwestern and co-lead author of the study, said the findings were dramatic but raise many additional questions.

"The animals in this study developed obesity mainly because they didn't produce enough heat after eating, not because the animals ate more or were less active," Dr. Xu said. "A better understanding of this pathway in the brain might lead to ways to activate or enhance it, and perhaps result in a way to combat obesity, not by prohibiting eating or increasing physical activity, but by generating more energy expenditure."

The next step, Dr. Elmquist said, is to identify the precise relationship between PI3 kinase-expressing neurons and fat-burning.

Brain chemical serotonin may help ward off diabetes

S erotonin – a brain chemical known to help regulate emotion, mood and sleep – might also have anti-diabetic properties.

The findings, which appeared in Nature Neuroscience, also offer a potential explanation for why individuals prescribed antipsychotic drugs that affect serotonin signaling sometimes have problems with their metabolism, including weight gain and diabetes.

"In this paper, we describe a circuit in the brain that may explain the anti-diabetic actions of serotonin-receptor signaling," said Dr. Joel Elmquist, professor of internal medicine and pharmacology at UT Southwestern and senior author of the study. "This discovery tells us that drugs that affect serotonin action can have anti-diabetic actions independent of body weight and feeding."

For the current study, the researchers engineered a mouse model in which the expression of a serotonin receptor called 5-hydroxytryptamine 2C was blocked throughout the body. Without functioning receptors, the mice developed insulin resistance in their livers.

Previous research has implicated these receptors in the brain in the regulation of energy balance and glucose metabolism throughout the body. When activated by serotonin, this receptor also is known to suppress appetite. Until now, however, it was unclear which type of neuron in the brain mediated the effects of serotonin to regulate glucose, or blood sugar, levels.

To find out, the study authors engineered another set of mice in which the same serotonin receptor was blocked everywhere except within a group of brain cells called pro-opiomelanocortin, or POMC, neurons. The POMC neurons, which are found in the hypothalamus, are also known to play an important role in suppressing appetite and inducing weight loss.

The researchers found that when they reactivated the serotonin receptor only in the POMC neurons, the mice no longer displayed insulin resistance in the liver.

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Healthy Bites
Go dark for a healthy heart

The Research suggests that drinking a cup of dark hot chocolate can be equated with drinking a glass of wine in protecting the heart, as long as it’s in moderation.

“Chocolate by itself may provide some health benefits,” says Lona Sandon, a registered dietitian at UT Southwestern. “It’s what is added to it that’s not so good for us.”

If you can’t resist eating chocolate or giving it as a gift, you should know that choosing the right type of chocolate can benefit your heart.

Pure chocolate, made from cocoa beans, is rich in flavanol, an antioxidant that may help protect arteries from damage, maintain healthy blood flow and fend off heart disease.

Dark chocolate and baking cocoa are excellent sources of polyphenols because most of the original cocoa bean remains. Chocolate in its more processed form, however, is loaded with extra oils, milk and sugars, lowering its level of polyphenols.

A bar of dark chocolate weighing about 1.5 ounces contains approximately 950 milligrams of antioxidants; a similar bar of milk chocolate contains only about 400 milligrams. White chocolate is a confection of fat and sugar and contains no antioxidants. Candy bars and boxed chocolates may be tasty, but their added fat and calories make them less healthy treats, Ms. Sandon says.

Cutting salt is a good idea

As Americans consume more and more sodium, federal regulators have begun urging food manufacturers to cut back on the amount of salt they add to everything from breakfast cereals to soups.

Plans are still under way, but the idea is that manufacturers would reduce the amount so gradually that consumers would barely notice the difference. The final limits have not yet been determined.

Dr. Jo Ann Carson, professor of clinical nutrition at UT Southwestern, said that reducing the salt added in food processing and restaurant food is a good idea. “It will make it easier for Americans to lower their salt intake,” she said.

The average American eats about 1 1/2 teaspoons of salt a day, more than twice the daily recommended limit.

“Lowering our salt intake is important to control blood pressure,” Dr. Carson said. “As Americans age and become more ethnically diverse, it becomes even more important to keep the salt under control.”

HUNGRY FOR KNOWLEDGE

Continued from page 2

Once hailed as a miracle weight-loss drug, Fen-phen was removed from the market more than a decade ago for inducing life-threatening side effects, including heart valve lesions. By using mouse genetics, UT Southwestern scientists, including Dr. Elmquist, have potentially identified the circuit in the brain that explains the ways fenfluramine, a component of Fen-phen, suppresses appetite.

“We’ve been able to show that this same circuit also controls your glucose levels in addition to your body weight,” said Dr. Elmquist, holder of the Maclin Family Professorship in Medical Science, in Honor of Dr. Roy A. Brinkley. “Without the mice genetics, we would not have been able to figure this out.”

More recently, Dr. Elmquist said his lab started an initiative to understand how bariatric surgery works.

“For better or for worse, bariatric surgery is the best treatment available for our patients right now for treating obesity and diabetes, but no one understands why it is so effective,” he said.

“Our goal is to understand the genes and brain circuits involved in order to figure out why bariatric surgery works, because it clearly does.”

SEROtonIN

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Dr. Elmquist, who holds the Maclin Family Professorship in Medical Science, in Honor of Dr. Roy A. Brinkley, said that even though the findings are in mice, they provide potential insight into blood glucose control in humans.

“It also further reinforces our previous findings that specific subsets of POMC neurons within the brain are responsible for the regulation of liver function and blood sugar metabolism,” he said.

The next step, he said, is to determine what happens to feeding, body weight and liver metabolism in mice engineered to lack this serotonin receptor only in the POMC neurons.
A Question of Nutrition? ........................................... Ask Dr. Carson

Q: Should I count total calories or only calories from fat?
A: If you are going to count, I suggest counting calories. When we became “fat-phobic” in the past, we sometimes lost sight of the calories and poor nutrition we took in as refined carbohydrates. If you are more visual than numbers-oriented, you will still need some math skills to look at your plate. Try to eat a plate that has only one-fourth lean protein and one-fourth starch (preferably with some fiber); the remaining half of your plate can contain lower-calorie veggies, such as green beans, broccoli, cauliflower, greens or salad. Add a nonfat dairy product, such as a glass of nonfat milk or a serving of nonfat yogurt or cheese, and you have a healthy meal that will likely keep you in energy balance. While you are counting, remember to add in at least 30 minutes of moderate physical activity daily to make energy balance easier.

Q: I have cut down on as much fat as I can, but my cholesterol is still high. What do you suggest I do next to reduce my cholesterol level?
A: To lower your total and low-density lipoprotein, or “bad,” cholesterol levels, focus on cutting down on saturated fat, not necessarily all fat. In addition to reducing saturated fat from animal foods like cheese, ice cream, sausage and poultry skin, you can add foods that lower blood cholesterol. These include high-fiber foods such as oatmeal, barley, dried beans, eggplant and okra. Consider substituting foods fortified with plant sterols, like margarine spreads, orange juice and even specialty milk.

Q: How many calories does the average alcoholic beverage have? And is it typical for drinkers (depending on amount) to gain or lose weight?
A: A standard serving of alcohol is defined as containing 0.6 grams of alcohol. That can be either a 12-ounce beer with 144 calories, a five-ounce glass of wine with approximately 100 calories or a jigger (1.5 ounces) of 80 proof distilled spirits. The calories in the beer can be reduced by choosing “light” beer containing about 100 calories. On the other hand, sweet liqueurs contain more calories; a jigger of crème de menthe, for instance, has 186 calories. What you mix in a mixed drink can add many calories. For instance, a 4.5-ounce piña colada contains 245 calories. On the other hand, diet soda with a jigger of rum still has only about 100 calories.

Weight is not directly related to alcohol consumption, perhaps because we drink alcohol in many different ways. Based on my observations, I see patients who add a six-pack of beer on the weekend to an otherwise energy-balanced diet and gain weight, sometimes becoming obese. On the other hand, someone with an alcohol dependence who drinks heavily may forgo almost all food and become thin. Individuals who consume alcohol according to the recommended levels of a maximum of one to two drinks per day and do so within the context of a healthy meal are likely to be near a healthy weight.
Make the Friends of the Center for Human Nutrition a part of your balanced information diet

Joining the friends makes you part of the effort to improve the quality of life today and for the future. As heart disease, obesity and diabetes become almost daily headline issues, the Center's work becomes increasingly more important. Your membership will support the research of promising young scientists and ensure that excellent nutrition research continues well into the future. Your membership also entitles you to receive the Center for Human Nutrition Newsletter and the Fresh News postcard four times a year, to attend regular meetings with other members and distinguished nutrition scientists, and to receive letters from Dr. Scott Grundy clarifying and updating current nutrition issues.

Annual membership in the Friends is a tax-deductible contribution of $1,000 per individual or couple. Membership in the Younger Friends, which has activities oriented toward those 40 or younger, is $250. A category has been added to the Younger Friends for those who are 41 to 45 years of age and that fee is $500 per year. To join the Friends of the Center for Human Nutrition, call 214-648-2344 or access our website at www.utsouthwestern.edu/donatenow.

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