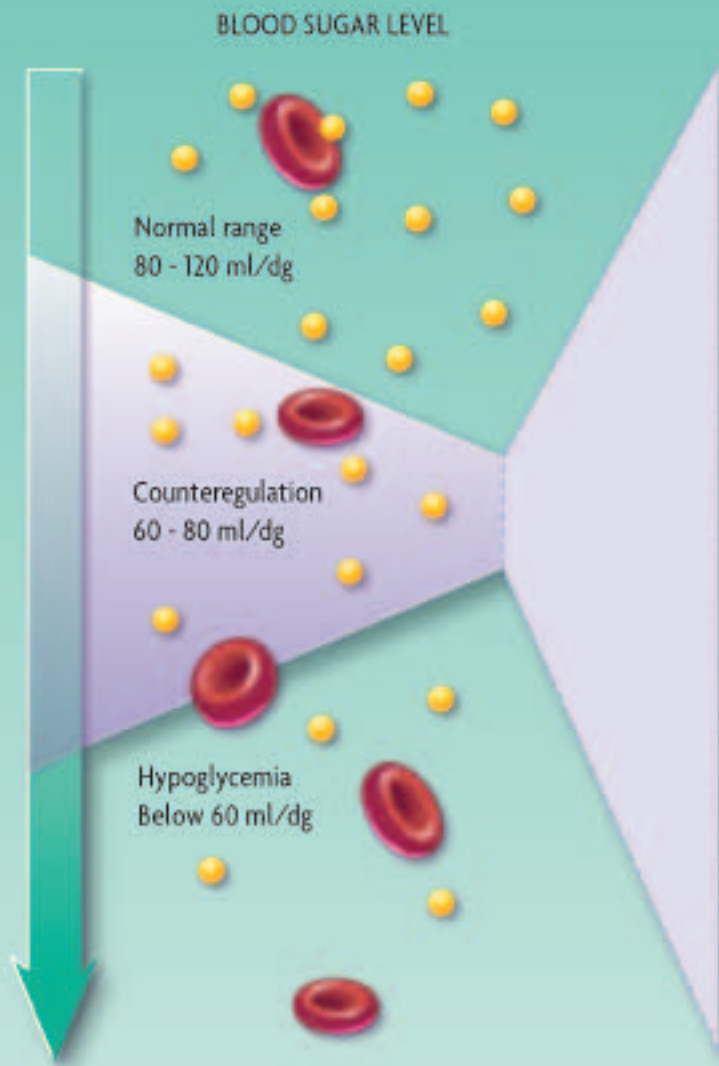


WHAT'S MAKING IT SO TOUGH TO AVOID HYPOGLYCEMIA?



By Robert S. Dinsmoor

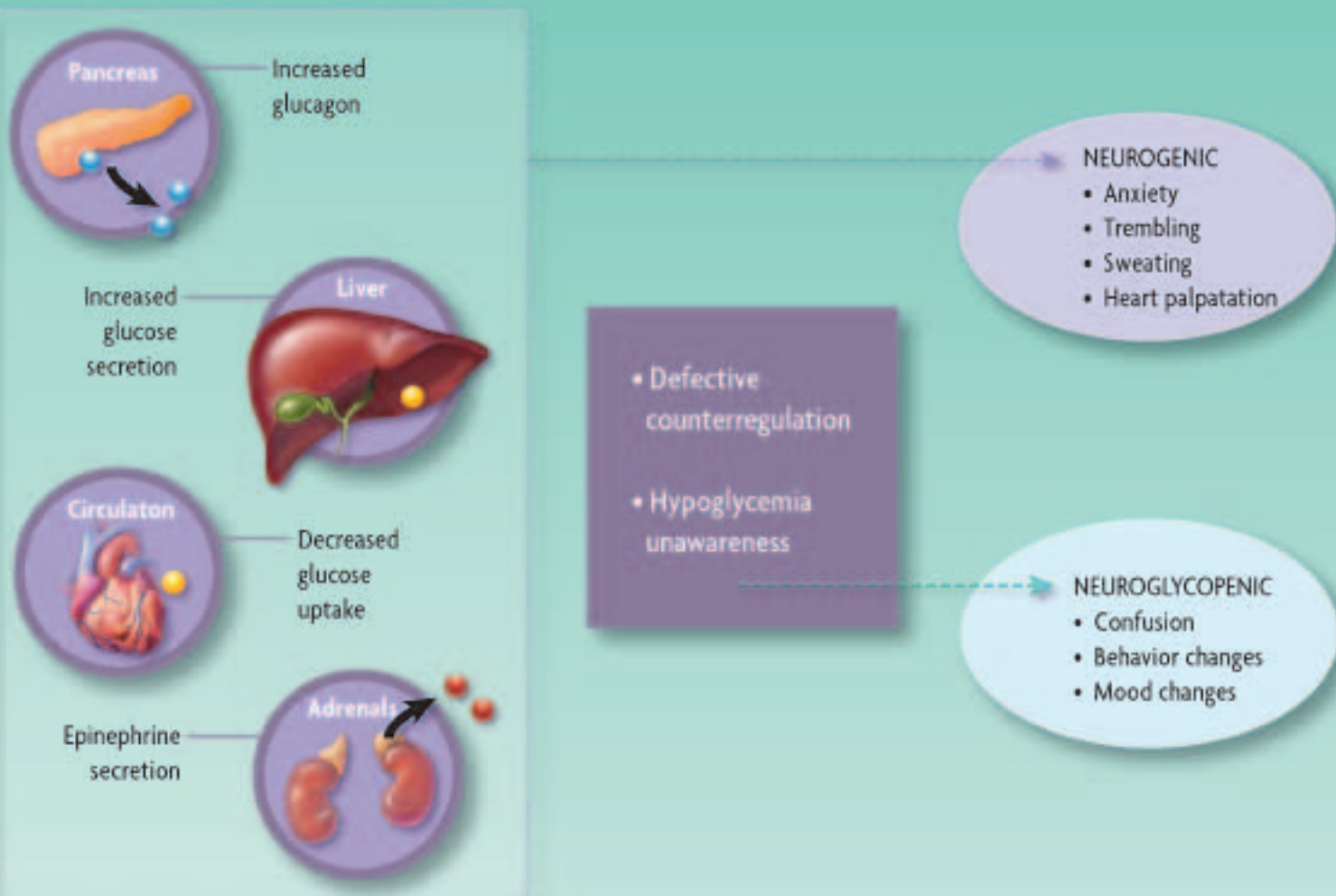
Illustration By Jennifer E. Fairman

People who have type 1 diabetes know the signs all too well: anxiety, trembling, heart palpitations, sweating, hunger. Without immediate treatment (usually some form of glucose ingested orally), symptoms can quickly become more insidious: difficulty thinking, confusion, behavioral changes, and mood swings. At worst, without glucose, a severe hypoglycemic episode can lead to seizures or loss of consciousness, even death.

What happens when blood sugar levels fall depends a lot on the autonomic nervous system—a system that takes many of its cues from the brain, and the brain, under normal conditions, feeds almost exclusively on glucose. Normally, the autonomic nervous system kicks in quickly as blood sugar levels begin to fall, triggering a series of complex reactions to counteract the effects of insulin, slow down the rate of glucose consumption, and release supplemental glucose from internal stores. Counterregulation is a near perfect natural defense against hypoglycemia in people who don't have diabetes. But in people with type 1 diabetes—especially those trying to achieve near normal blood glucose levels through tight

COUNTERREGULATION

SYMPTOMS



control and intensive insulin therapy—the autonomic nervous system often fails to respond appropriately to falling blood sugar levels. Sometimes, it doesn't seem to respond at all.

For more than a decade, researchers have known that tight blood glucose control can dramatically reduce the risk of diabetes-related complications (eye disease, kidney disease, and nerve disease), but tight control carries a threefold higher risk of hypoglycemia.

“We asked parents of children with diabetes what they fear most, and at the top of the list was hypoglycemia. Even if you ask most of the adults I treat, their fear is hypoglycemia,” says Robert Sherwin, M.D., C.N.H. Long professor of medicine at Yale University School of Medicine and director of the JDRF Center for the Study of Hypoglycemia at Yale University in New Haven, Connecticut. “People with type 1 diabetes have to face a double-edged sword. Namely, if they don't control their blood glucose aggressively, there are serious long-term complications, and if they do, it's almost impossible to avoid hypoglycemia.”

What concerns researchers most is that two conditions—both of which result in more frequent and/or severe episodes of hypoglycemia—seem to occur most often in people who are tightly controlling their blood sugar levels. Known as hypoglycemia unawareness and defective counterregulation, both conditions affect how the body senses and responds to falling blood glucose levels.

Current research efforts have scientists focused intently on how the body senses low blood glucose levels and how and why it naturally responds to make an appropriate correction. What causes these defense mechanisms to fail in people who are trying to achieve tight control? How does hypoglycemia affect brain function? How much does the brain have to do with sensing low blood sugar levels and telling the body to respond? Most important, researchers are trying to figure out what can be done to protect people with diabetes from hypoglycemia.

SENSING LOWS: SIGNS AND SYMPTOMS



MIRANDA DEPLOI, 14

Miranda DePloi, 14, an eighth-grader in Brookfield, Connecticut, has had type 1 diabetes for nearly 10 years. Occasionally, severe hypoglycemia causes her to become very confused. “There are times I’ve been really, really low when I woke up for school and couldn’t figure out how to put my glasses on. Sometimes I’ve tried to put my clothes on over my pajamas. There have been times I’ve tried to eat something and kept missing my mouth and getting it all over myself,” she recounts.

Once DePloi had a severe low during a 20-minute bus ride to school and didn’t have any juice to drink. Fortunately, her twin sister, Brittany, kept her awake throughout the bus ride, until the girls got to school where Miranda could eat something.

A member of the soccer team, the basketball team, the track team, and the swim team at school, DePloi admits that hypoglycemia can be annoying during sports. “My parents won’t let me back in the game until I’m above 70,” she says. “That’s annoying—but of course they’re right!”

Her advice to others: “Kids with diabetes should tell others they have diabetes because their friends are the ones who can rescue them from lows.”

Associated with the autonomic nervous system’s “flight or fight” response, symptoms like anxiety, trembling, sweating, and heart palpitations are known as *neurogenic*, and commonly occur when blood sugar levels begin to fall below normal. Another type of symptoms, called *neuroglycopenic* symptoms, most often occur during more severe hypoglycemia. These symptoms are associated with brain function. Unlike other parts of the body, where tissues store a form of glucose called glycogen, the brain relies solely on glucose in the bloodstream for fuel. When it is starved for glucose,

the brain cannot function properly, creating such symptoms as confusion, behavioral changes, and mood swings.

The human body is equipped with several mechanisms to prevent hypoglycemia. In a feedback loop (much the same way a thermostat works), the pancreas reacts to low blood sugar levels by decreasing insulin secretion. If the blood glucose level continues to drop, a series of events (collectively called counterregulation) kicks in. Alpha cells in the pancreas secrete more of a hormone called glucagon, which works against the action of insulin. Glucagon also

signals the liver to manufacture and secrete more glucose. At the same time, the adrenal glands secrete increased levels of a hormone called epinephrine. In addition to stimulating the manufacture and secretion of glucagon by the liver, epinephrine keeps the body's tissues from using as much glucose. (Epinephrine is thought to cause some of the neurogenic symptoms of hypoglycemia—namely, the anxiety, trembling, and heart palpitations.)

The secretion of growth hormone and cortisol also increase, which increases glucose production and limits glucose utilization, but only over a period of hours. This system of counterregulation is virtually unailing in people who don't have diabetes.

"Individuals with type 1 diabetes lose two, if not three, of these defense mechanisms," notes Stephen Davis, M.D., Rudolph Katmeier Professor of medicine and molecular physiology and biophysics and chief of the division of diabetes, endocrinology, and metabolism at Vanderbilt University School of Medicine in Nashville, Tennessee. "Since their pancreases no longer make insulin and they must inject it, there is no way to decrease the level of insulin in the bloodstream after it's been injected. The second defect is that, after about five years of diabetes, the alpha cells of the pancreas no longer release glucagon in response to hypoglycemia. That leaves patients totally dependent on the epinephrine response. Yet, what happens in intensively treated [tightly controlled] individuals with diabetes is that the epinephrine response is reduced so that the blood glucose level must fall much lower before the epinephrine response occurs. This condition, known as defective counterregulation, puts people at a 25-fold greater risk for severe hypoglycemia."

Defective counterregulation is often observed in patients with hypoglycemia unawareness, a condition that prevents people from experiencing the early "uncomfortable" warning signs that normally accompany falling blood sugar levels. Since they are no longer able to sense impending hypoglycemia, people with hypoglycemia unawareness are unable to take measures to counteract low blood sugar levels on their own (i.e., ingesting some form of glucose). These individuals can progress from seemingly normal to a state of severe hypoglycemia with no warning. They can become confused, disoriented, or lose mental focus in a matter of moments. The condition is associated with life-threatening risks, such as an increased risk of passing out while driving or operating heavy machinery. Hypoglycemia unawareness is thought to be the result of a blunted autonomic nervous system response. Researchers also believe that, like defective counterregulation, hypoglycemia unawareness results in part from a reduced epinephrine response.

HYPOGLYCEMIA BEGETS HYPOGLYCEMIA—BUT WHY?

In the early 1990s, Philip Cryer, M.D., Karl Professor of Endocrinology and Metabolism at Washington University School of Medicine in St. Louis, and colleagues discovered that "hypoglycemia begets hypoglycemia." In other words, a recent bout of hypoglycemia could promote both defective glucose counterregulation and hypoglycemia unawareness. They dubbed this phenomenon "hypoglycemia-associated autonomic failure." Conversely, they have discovered that scrupulously avoiding hypoglycemia for as

EXERCISE AND HYPOGLYCEMIA

"We're big advocates of exercise and we think all our patients should be exercising, but clearly in type 1 diabetes, there's this nasty exercise-related hypoglycemia. It can happen during exercise, 1 to 2 hours after exercise, or even 17 to 21 hours after exercise," says Stephen Davis, M.D., Rudolph Katmeier Professor of medicine and molecular physiology and biophysics and chief of the Division of Diabetes, Endocrinology, and Metabolism at Vanderbilt University School of Medicine in Nashville, Tennessee.

In the past, researchers thought that this particularly vexing form of hypoglycemia—which could be severe and could happen so long after exercise—was solely due to the fact that exercise makes the body more sensitive to insulin. While enhanced insulin sensitivity undoubtedly plays a role, says Dr. Davis, another explanation may be that exercise reduces the counterregulatory response. "We've done a whole series of experiments looking at the effects of prior hypoglycemia on the ability to maintain glucose during exercise, because the physiologic responses during exercise and during hypoglycemia are pretty similar. What we find in both healthy individuals and those with type 1 diabetes is that, if you get hypoglycemia today, that reduces your ability to protect your glucose during exercise the next day. Similarly, if you have exercised today, that reduces your ability to defend against hypoglycemia tomorrow. So, we actually think there's a feed-forward reciprocal vicious cycle going on between exercise and hypoglycemia."

Funded by a JDRF grant, Pietro Galassetti, M.D., Ph.D., assistant professor of pediatrics and medicine and director of the bionutrition and metabolism core at the Clinical Research Center of the University of California-Irvine, is looking at this problem in children. "I'm trying to correlate exercise with overnight hypoglycemia in the long run. Children are not necessarily carbon copies of what happens in adults. There are added variables, such as growth hormones and certain cytokines that are found at high levels in children and may play a role in nocturnal hypoglycemia, and we're trying to define those mechanisms," says Dr. Galassetti.

Dr. Davis doesn't believe that people with type 1 diabetes should shun exercise over fears of hypoglycemia. But they do need to take certain precautions to protect themselves during and after exercise:

- Reduce basal insulin before exercise.
- Eat right after exercise in order to replenish glycogen stores.
- Consider decreasing preprandial (or bolus) insulin before the next meal.
- In the 24 hours following exercise, especially if exercise was more intensive than usual, it may be helpful to set target blood glucose levels higher—say, 20 mg/dl higher.

little as two or three weeks can improve the reduced epinephrine response, thus improving defective glucose counterregulation and hypoglycemia unawareness in affected individuals.

Can scrupulously avoiding hypoglycemia restore effective glucose counterregulation in the real-world setting? Not everyone agrees, but some experts think it can. "It has certainly been done in research studies," says Stephanie Amiel, M.D., professor of diabetic medicine at King's College in London. "It does, however, require a lot of attention on the part of the patient and a lot of support from the healthcare professional."

According to Dr. Amiel, the trick to avoiding hypoglycemia is

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not to ease up on blood glucose control. “I think what you have to do is to devote as much attention to avoiding the lows as you do to avoiding the highs. This is done quite often by intensifying insulin regimens, using some of the new insulin analogs, or pump therapy,” she says.

What causes hypoglycemia-associated autonomic failure in the first place? No one knows, but a number of hypotheses are being studied. According to Dr. Sherwin, one basic premise is that the brain somehow adapts to low blood sugar in order to protect itself and, feeling “safe,” doesn’t signal the autonomic nervous system and epinephrine responses. First, the brain appears to become more efficient at drawing glucose out of the bloodstream. Second, it may alter the type of fuel it uses. “Our data suggest that the brain adapts to a lot of hypoglycemia by becoming less dependent on glucose and more dependent on other fuels, such as lactic acid, small- and medium-chain fatty acids, and other fuels that can serve to keep the brain functioning at a basic level. It may not be best for cognition, which is probably more dependent on glucose. Our studies indicate that what happens is that the brain adapts so that it delivers fuel to the critical areas of the brain that are responsible for controlling respiration and all basic functions and it compromises higher cognitive function,” explains Dr. Sherwin.

The fact that the brain can defend itself by switching fuels opens up the possibility of protecting the brain, especially at night. “It may be that we can supply an alternative fuel as a way of protecting the brain from the harmful effects of hypoglycemia without affecting blood glucose levels. So, people could probably take something at night that would not raise their glucose but protect their brain if glucose fell,” says Dr. Sherwin.

Another proposed mechanism behind hypoglycemia-associated autonomic failure has to do with the hormone cortisol, which is released into the bloodstream during hypoglycemia, but also during exercise and emotional stress. “When you have hypoglycemia, you release a whole concerto of hormones and other substances, and one of them is cortisol,” Dr. Davis explains. “Cortisol doesn’t have a major role in the defense against acute hypoglycemia, as far as reining in blood glucose. What we and others have found is that cortisol can in fact turn down the nervous system to subsequent hypoglycemia. The question is whether it’s physiologically relevant: Is it only in the high physiologic range that it can do this, or can small amounts of cortisol that are reached during everyday hypoglycemia do this? And there’s evidence for and against.”

In fact, according to Dr. Davis, the cortisol that is released during exercise may account for the fact that exercise also seems to downregulate the autonomic nervous system. (See “Exercise and Hypoglycemia” on page 21.)

Dr. Sherwin believes that the actual culprits may be two stress hormones in the brain, namely corticotropin-releasing hormone (CRH) and neurocortin, which interact with cortisol. “When you get stressed, CRH and neurocortin are activated, and that tells the

NIGHTTIME HYPOGLYCEMIA

Travis Blinn, 14, rarely even remembers the severe hypoglycemic episodes he has at night, but his mother Ginny does. She has seen him have seizures, and she has been there to treat him by rubbing jelly, honey, or glucose gel inside his cheeks. All Travis notices is that he wakes up with bad migraine headaches.

Nighttime hypoglycemia is a common problem among children and adolescents with type 1 diabetes, and at least one study has suggested that autonomic responses to hypoglycemia are blunted during sleep and that may make them less likely to be awakened by hypoglycemia. Yet, while it’s important to recognize the problem and try to prevent it, some parents become obsessed with it, according to JoAnn Ahern, A.P.R.N., M.S., C.D.E., coordinator of the Yale Program for Children with Diabetes. “Some parents are up all night, checking their kids’ blood sugar, and I don’t think that’s good for anybody. I think it makes the kids afraid. What they may not realize is that eventually the child’s liver will secrete glucose, and they’ll wake up. They may have a headache and feel lousy, but they’re going to be all right,” she says. “The other thing I see is running the blood sugar levels high at night to avoid hypoglycemia. But you still have lows when you do that, so I don’t think that’s the way to manage it.”

Ahern offers some more practical strategies for dealing with nocturnal lows: Those taking insulin injections may need to have a bedtime snack with a fair amount of protein in addition to carbohydrate to carry them through the night. In children using insulin pumps, the overnight basal rate may need to be decreased during the hours when hypoglycemia typically occurs.

body to release a lot of things to protect it against stress. But repeated stress leads to downregulation of these hormones, because if the body didn’t adapt to stress that was coming continuously, it would just become stressed out. My guess is that this system becomes downregulated by recent hypoglycemia,” offers Dr. Sherwin. “I think that the stress hormones that the body normally uses to adapt to stress are probably altered. There may be alterations in the sensing mechanisms and the fuels that the brain uses. And all of these things have an impact on unawareness and defective glucose counterregulation. So, I don’t think it’s one thing, but that multiple factors are involved. And we’re doing our best to unravel what is probably a complex story.”

IN SEARCH OF THE GLUCOSE SENSORS

To determine the root causes of hypoglycemia unawareness and defective glucose counterregulation, researchers are trying to identify and understand the “sensors” the body depends on to detect hypoglycemia—where they are, how they work, and how they might malfunction in people with diabetes. “If you’re looking for a hypoglycemia sensor in the body, you would logically ask, ‘What parts do I need to protect from hypoglycemia?’ As it turns out, very important sensors—and possibly the most important hypoglycemia sensors—are in the brain,” explains Dr. Amiel. “A lot of work has been done recently on individual nerve cells that have the ability to sense glucose. These cells not only use glucose for fuel, but also use the glucose to tell them whether or not to fire. There are networks



TRAVIS BLINN, 14

Travis Blinn, 14, of Wallingford, Connecticut, has had type 1 diabetes since he was 5 years old. Due to hypoglycemia unawareness, he has had episodes of severe hypoglycemia at night, causing seizures and requiring his mother to rub glucose gel into his cheeks to bring him around again.

Hypoglycemia sometimes causes the normally good-natured teenager to become argumentative when his mother insists he's low and tries to get him to drink some juice. Occasionally, going low in class causes him to become confused when the teacher calls on him, bringing unwelcome attention from classmates.

of nerve cells in the brain that are activated or turned off according to the amount of glucose they detect in the blood. And many of them are located in a part of the brain called the hypothalamus.”

Using a number of ultra-high-tech tools, Dr. Sherwin and his research team have been studying brain metabolism in people with diabetes and how it is affected by intensive treatment and tight blood glucose control. “Our data suggest that the critical area of the whole system is the ventromedial hypothalamus, an area at the base of the brain that plays a critical role in the feeding response,” he says. Research findings indicate that these brain cells may sense

Yet, hypoglycemia unawareness hasn't kept Blinn from riding dirt bikes, skateboarding, or playing basketball. He tests his blood sugar levels frequently and eats crackers or drinks juice as a precaution before he plays basketball or goes out skateboarding.

Blinn's advice to other children who have the same condition: “Just monitor your blood sugar as often as you need to. And if you start to feel different, you should test your blood sugar level right away. Take good care of your diabetes now to make sure something bad doesn't happen over the long term.”

glucose much in the same way as the insulin-secreting beta cells of the pancreas do.

Dr. Sherwin's research has revealed two chemical pathways that may contribute to glucose sensing in the brain. One involves glucokinase, the same enzyme that pancreatic beta cells use to sense glucose levels. Research at the JDRF Center at Yale currently includes studies to manipulate glucokinase to see whether this will affect glucose sensing.

A second pathway under investigation by Dr. Sherwin and his research team involves an enzyme called AMP kinase. “AMP kinase

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is thought to be a fuel sensor. In the muscle, for example, if you're developing a fuel deficit, AMP kinase is activated and promotes more fuel to go into the muscle," Dr. Sherwin explains. "This enzyme actually causes cells to use fat instead of glucose. And what's interesting about that is that we always thought that the brain could only use glucose. However, in an emergency situation, it may be able to use fat. So, we believe that there are two sensing mechanisms, one dependent on glucokinase that probably becomes abnormal during hypoglycemia, and another one probably dependent on AMP kinase, which is a more primitive backup system to alert the brain to fuel deficit."

Like Dr. Sherwin and Dr. Amiel, most experts are convinced there are probably multiple glucose sensors throughout the brain and body, but their relative importance is unknown. Dr. Amiel has been exploring the possible role of sensors located in the hepatic portal vein, which carries nutrients absorbed from the gastrointestinal tract to the liver. Earlier studies have shown that, when laboratory rodents are made hypoglycemic, infusing glucose into the portal vein turns down the counterregulatory response. This would indicate that an exclusive blood glucose sensing and response system exists in the hepatic portal vein.

With funding from JDRF, Dr. Amiel and colleagues have been studying this same effect in humans. After administering a glucose-rich drink to nondiabetic study volunteers, the researchers administered enough insulin to cause hypoglycemia. Since ingested glucose goes straight into the portal vein, patients experienced hypoglycemia throughout the rest of the body—but not in the portal vein. As it turned out, keeping blood glucose levels higher in the portal vein blunted the counterregulatory response. The results of the study were published in the journal *Diabetologia* in 2002.

"The data we have suggest that there is a portal vein hypoglycemic sensor in humans, and it does work, but it certainly isn't the major hypoglycemic sensor. It's almost as if the brain is doing the main sensing, but the portal vein can actually see if glucose is coming in from the gut and tell the brain that glucose is coming and to knock down counterregulation a bit," Dr. Amiel explains.

PROTECTING THE BRAIN FROM HYPOGLYCEMIA

While transient episodes of mild hypoglycemia do not appear to have long-term effects on brain function, doctors are concerned about the long-term effects of prolonged, severe hypoglycemia—as when someone lapses into a coma. "If severe hypoglycemia persists for a long enough period of time, there will be death of neurons in the brain. Some neurons are more sensitive than others, and the ones that are most sensitive to hypoglycemia are the ones involved in learning and memory," according to Raymond Swanson, M.D., professor of neurology at the University of California–San Francisco School of Medicine and chief of neurology and rehabilitation services at the San Francisco VA Medical Center.

How can the brain cells be protected? Drugs called PARP inhibitors are currently being tested in patients with cardiac ischemia and stroke to see whether they can protect the brain's neurons from damage inflicted by the loss of blood flow to the brain.



The enzyme poly ADP-ribose polymerase (PARP) is ordinarily activated when DNA within cells is damaged.

"When it finds broken strands of DNA, PARP attaches long polymers of ADP ribose to nearby proteins as a way of marking the site as a site of DNA damage. It initiates a complicated series of steps to make sure the DNA is repaired properly. The process of making these ADP ribose polymers requires a lot of energy, and it consumes substrates in cells—which is not a big deal when you have one or two breaks in your DNA. But what happens with stroke or severe hypoglycemia is that there's massive DNA damage and massive activation of PARP, and now you've got problems. PARP inhibitors may protect brain cells by interrupting this vicious cycle," says Dr. Swanson. "Another way of looking at this is that, at high levels, PARP is a way of inducing cell suicide. Your body doesn't want to have a lot of cells with DNA damage because that can cause cancers. So, in a cell that has a lot of DNA damage, the PARP collects there and triggers the cell suicide mechanism. And it's not clear which of these hypotheses is true or whether in fact both are true."

Drugs that inhibit the action of PARP, given during or shortly after an episode of severe hypoglycemia, would be expected to protect brain cells from these destructive mechanisms without affecting the normal protective function of PARP over the long



RAUL CAMACHO, 26

Raul Camacho, 26, of Nashville, Tennessee, is currently working toward his doctorate in molecular physiology and biophysics at Vanderbilt University. He was diagnosed with type 1 diabetes when he was 5 years old. Although he has been experiencing lapses in concentration for years, it was only when he started working with diabetes researchers that he found out there was a name for it: hypoglycemia unawareness.

“I’ll be reading a paper, looking at data, and suddenly realize it isn’t making any sense to me. It’s just not clicking. My immediate response is that my blood sugar is low—and when I check it, nine out of ten times it is,” he says.

Camacho says hypoglycemia unawareness hasn’t interfered with his ability to pursue a career in medical research or with his outside activities. In addition to being a graduate student, he’s a musician, DJ, soccer player, and Vespa motor scooter enthusiast. The biggest disadvantage to having hypoglycemia unawareness, he says, is that it has put a bit of a strain on his work and personal relationships.

“It can be distracting and frustrating, but there’s something to be said for knowing and understanding that hypoglycemia unawareness is what causes me to lose focus. I can address it,” says Camacho, who will be relocating to New York soon to work with a leading diabetes researcher. “I’ve had a great cultural and social life with my music. I was able to tour the country. I love soccer and play it all the time. I’ve never let diabetes or hypoglycemia hinder me in any way.”

term. To test whether PARP inhibitors could actually protect brain cells from severe hypoglycemia, Dr. Swanson and colleagues treated laboratory rats with insulin to make them severely hypoglycemic for a 30-minute period. At the end of this 30-minute period, they injected the rats with either glucose alone or glucose and a PARP inhibitor. In some cases, they delayed the injection of the PARP inhibitor by one, two, or three hours to find out what effects this delay would have.

The researchers assessed the effects of hypoglycemia and the PARP inhibitor in two ways. In some cases, they examined the rats’ brains a week later to see what percentage of neurons had survived in the most vulnerable area, the hippocampus. In other cases, they gave the rats learning and memory tests six weeks later.

In the animals that did not receive the PARP inhibitor, about 50 percent of the neurons in the hippocampus died. In those rats treated with the PARP inhibitor along with the glucose, only 10 percent of the neurons died.

“When we gave the drug an hour later, there was still about a 50 percent reduction in cell death. If we gave it two hours later, there was a minor effect. And if we gave it three hours later, there was no effect at all,” says Dr. Swanson. The rats that received the PARP inhibitor at the same time as the glucose did as well on the learning

and memory tests as rats that had not been made hypoglycemic, whereas the rats that did not receive the PARP inhibitor fared poorly.

“This study really establishes the fact that neuron death is not an inevitable consequence of severe hypoglycemia,” says Dr. Swanson. “The other thing that is exciting is that the study mimics what might happen if a patient comes into the emergency room with severe hypoglycemia. It might take the hospital team a while to find the drug and give it to the patient. We found that, if we give the drug as much as an hour later, there is still a very large effect.”

THE RESEARCH HORIZON

Dr. Sherwin, who has been studying hypoglycemia since he was a pioneer of insulin pump therapy in the late 1970s, sees a new era emerging in the study of hypoglycemia. “Until the last few years, there were neuroscientists who were interested in the brain but had no interest in diabetes, and there were diabetes researchers who were interested in the brain but had no experience in neuroscience. The goal of our center has been to bring these camps together,” he explains. “I think we’re really at a very exciting phase in terms of understanding how the brain works and being able to help people with diabetes by finding out how the brain is adapting to hypoglycemia.”