COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Mechanisms for restoration of hypoglycemia awareness
NCT03738852

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Funding Source: NIH/NIDDK

Healthy Control Participants

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at mechanisms for restoration of hypoglycemia awareness. You have been asked to take part because you are a healthy person without type 1 diabetes mellitus (T1DM).

To decide whether or not you wish to be a part of this research study you should know enough about the risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be done, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Study Description

Individuals with Type 1 diabetes often have episodes of low blood sugar called hypoglycemia. Frequent episodes of hypoglycemia can lead to the development of unawareness that blood sugars are low, which may prevent the individual from treating the low blood sugar appropriately. The mechanisms underlying why this happens remain unclear. Thus, the main aims of this study are 1) to determine the impact of frequent hypoglycemia and hypoglycemia unawareness on brain responses to visual food pictures as well as at rest in patients with T1DM; 2) to determine how frequency of hypoglycemia effects how glucose is transported and metabolized in the brain.

We plan to enroll individuals with T1DM who are either aware or unaware of hypoglycemia as well as healthy control participants.

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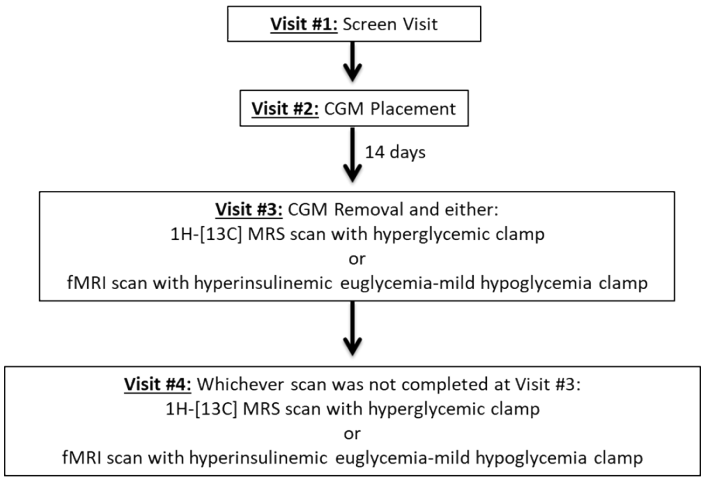
Study Procedures

If you agree to participate in this research study, there are a total of 4 study visits.



Visit #1: Screen Visit

You will be screened at the Yale New Haven Hospital (YNHH) Hospital Research Unit (HRU) or the Yale Center for Clinical Investigation (YCCI) Church Street Research Unit (CSRU) with a medical history, physical exam, and electrocardiogram (EKG). Blood work will be collected for A1C, liver function, TSH, electrolytes, renal function, CBC, and C-peptide. This visit will take approximately 1 hour.

If you are eligible after the screen visit, you will be asked to return for 3 more visits as follows:

Visit #2: Continuous Glucose Monitor (CGM) Placement

On the visit for CGM placement:

1) A study clinician will explain to you how to use the CGM (FreeStyle Libre Pro).
2) The CGM will be placed on your upper arm.
3) You will be asked to complete neurocognitive questionnaires.

This visit will take approximately 30 minutes at either the HRU or CSRU.

CGM:

CGM allows us to measure your glucose levels continuously throughout the day. The results will be blinded (you will not be able to see your glucose levels). We will ask you to wear the CGM for ~14 days prior to your first brain scan (either fMRI or MRS). It will be placed on your upper arm and attached with an adhesive patch by a trained study staff member. The sensor includes a wire-like tip which will be under your skin in your fat tissue. You will be taught how to use the CGM. The sensor is water-resistant and can be worn while bathing, showering, or swimming as long as you do not take it deeper than 3 feet (1 meter) and do not keep it under water for longer than 30 minutes at a time. Intense exercise may cause the sensor to loosen due to sweat or movement of the sensor. If the CGM sensor falls off while you are wearing it, we will ask you to return to the HRU or CSRU so that a new sensor can be re-inserted. Please contact us at 203-737-4777 or diabetes.research@yale.edu if you have any questions, concerns or issues related to the CGM.

Neurocognitive questionnaires: You will be asked to complete some questionnaires and tests on a computer or on paper to assess your cognitive function.

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Visit #3 and #4: fMRI or MRS scanning
Depending on scanner availability, you will undergo either fMRI or MRS scanning (detailed below). Whichever scan is not completed at Visit #3 will be done at Visit #4.

fMRI scan with hyperinsulinemic euglycemia-mild hypoglycemia clamp: You will arrive on the morning of the scan at the Yale Magnetic Resonance Research Center (MRRC) at the Anlyan Center (TAC) at ~7AM following an 8 hour overnight fast.

A nurse will place two intravenous (IV) catheters into your arms. Then, you will receive an infusion of insulin, the hormone that regulates blood sugar (glucose) levels, together with a variable glucose infusion to keep glucose levels at ~100-110 mg/dl. Once glucose levels are stabilized outside the magnet (~45 min), you will be transferred into the MRI where your blood sugar will initially be maintained at ~90 md/dl for ~60 minutes and then decreased to ~55-60 mg/dl for ~60 minutes. During the scanning, you will be asked to look at pictures of food and non-food images as well as complete some cognitive tasks. At each clamp step, you will also be asked to complete questionnaires assessing hypoglycemia. Throughout the visit, blood samples will be taken to measure glucose levels and hormones that play a role in regulating your blood sugar levels.

1H-[13C] MRS scan with hyperglycemic clamp: You will arrive on the morning of the scan at the MRRC at ~7AM following an 8 hour overnight fast. Following IV placements and baseline blood samples, at ~8 AM you will receive a low dose insulin infusion as well as variable glucose infusion to keep glucose levels at ~100-110 mg/dl for baseline scanning. Then, your blood glucose level will be increased to ~180 mg/dl using 1-13C-glucose for ~2 hours. Throughout the visit, blood samples will be taken to measure glucose levels and hormones that play a role in regulating your blood sugar levels.

Potential Risks
While in this study, you may have side effects. Expected side effects are listed here. In addition to the risks listed below, there may be risks that are currently unknown. If significant new information becomes known to us during the time you are on the study, we will tell you so you can decide if you should stay in the study. Possible side effects that you may experience during this study will be fully explained to you by the study staff. Please ask as many questions as you want so that you can understand the possible side effects before you decide whether you want to be in this study. Please ask the study clinicians or the study staff to explain any information or words that are not clear to you.

MRI/MRS:
Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x- rays, to take pictures and measure chemicals of different parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

You will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

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There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To lower this risk, all people involved with the study must remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.
We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information you think might be important.

This MR study is for research purposes only and is not in any way a health care examination of the brain. The scans performed in this study are not designed to find abnormalities. The principal investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a health care evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie only with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a health care MR exam and for that reason, they will not be made available for health care purposes.

Insulin and dextrose (glucose) infusion:
Intravenous (IV) catheters will be placed under sterile conditions by experienced staff members. All studies will be performed under the direct supervision of a physician or nurse practitioner. All solutions for infusion will be pyrogen free and prepared in a sterile environment.

The infusion of insulin and dextrose to achieve hypoglycemia can potentially result in symptoms of varying severity. You may experience little or no symptoms of sleepiness, hunger, anxiety, palpitations, diaphoresis, difficulty concentrating, mild confusion and/or tremor. There is a small risk that plasma glucose will fall below the predetermined level resulting in exaggerated symptoms. All such symptoms are rapidly reversible with an intravenous dextrose infusion. To avoid excess hypoglycemia, plasma glucose levels will be checked every 5 minutes using a bedside glucose monitor. Based on these measurements, the plasma glucose will be adjusted via the 20% dextrose infusion.

The infusion of dextrose to achieve hyperglycemia (~180 mg/dl) is not associated with any specific symptoms or significant adverse effects. This modestly high glucose level can be seen in poorly controlled diabetic patients following a meal. During the study, there is a small risk that plasma glucose may fall to lower levels resulting in symptoms of hypoglycemia.

13C glucose:
The infusion of 13C glucose involves no radioactivity, and the glucose is metabolized just as unlabeled glucose. Clinical research studies using 13C glucose have been used at Yale for decades with no adverse effects. The glucose solution is purchased from (Cambridge Isotopes, Inc.) in powder form which has been certified to be sterile and free of pyrogens. The glucose is made into a solution

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of 20gram/100 ml (D-20) by the Yale New Haven Hospital Investigational Drug Service (IDS). The solutions are tested to be free of pyrogens and to be sterile before being administered.

CGM:
The CGM poses no major risks to the users. The CGM catheter will be placed under sterile conditions by experienced staff members. You may experience bruising and bleeding of the skin at the insertion site of the CGM sensor. This minor condition will resolve by itself in a few days. You may feel a mild discomfort (pin prick sensation) during the sensor insertion. Redness and discomfort (infection and inflammation) can occur at the sensor insertion site. Some individuals may be sensitive to the adhesive that keeps the sensor attached to the skin. If you notice significant skin irritation around or under the sensor, please contact us and it can be removed. Rarely sensors may break and a small piece may remain under the skin which will need to be removed by the physician. This may cause mild discomfort, bruising, or temporary bleeding. You will be given one of the study physician or nurse practitioner's cell phone number to contact for any questions, concerns or problems. If you have an MRI, a CT scan, or diathermy treatment, you must remove your sensor prior to the procedure.

Phlebotomy:
Phlebotomy can result in anemia, although the amount of blood taken for these studies should not result in clinically-significant anemia. The total amount of blood taken as part of participation of this study will not exceed 24 tablespoons,, which is less than a typical blood donation. You will be excluded from participating in the study if your hemoglobin is less than 10 gms/dL. All subjects having donated blood within 30 days of the study will be asked to postpone study participation (with a repeat blood count prior to future enrollment), and you will be advised to refrain from blood donation for 30 days after study completion.

Blood Draw Chart

AIM 1 & AIM 2	Draw Amount	Days between Visits
Screen Visit	4 tbsp	
fMRI	9 tbsp	Typically approx. two weeks after screen visit
MRS	11 tbsp	Typically approx. two weeks after fMRI visit

Questionnaires:
The questionnaires are generally benign in nature. The major inconvenience is the time taken to complete them and a possible breach of confidentiality. Study participation is voluntary and you are free to drop out at any time without penalty. All data will be kept confidential except in cases of imminent danger to the participants. Good clinical and research practice procedures and HIPAA regulations will be followed. No subjects are identified by name in any of the published literature and only by code in major data storage areas.

Benefits

You will not directly benefit from participating in this study. However, this work will benefit the scientific community, and therefore society, as it will provide important insights into T1DM.

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Economic Considerations

You will be compensated as follows:

$25 for screening visit
$50 to wear CGM and complete questionnaires (with > 80% compliance/time points collected)
$175 for fMRI scan/hypoclamp (+ an additional $25 bonus depending on how you do at the tasks during the scan)
$200 for MRS scan/hyperclamp

Payments will be given to you via a Bank of America pre-paid debit card using the Yale electronic payment service. After your first payment milestone (the screening visit), you will receive a card in the mail which you will need to activate over the phone. Once you activate this card, all other payments during the study will go directly onto your card. Please note that your name, address, and telephone number will be shared with Bank of America for ePayments.

According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in this study may be considered taxable income.

Tests and procedures that are done for your regular care (whether you are in this study or not) are called "standard of care" and will be billed to you or your insurance company. There will be no charge to you or your insurance provider for tests or procedures done only for research purposes. You and your insurance provider will not have to pay for the MRI(s) or any blood tests that are done for research purposes.

Parking vouchers will be provided for all study related visits.

Treatment Alternatives

The alternative would be not to participate in the study.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases.

It is important for you to know that if you do not already have a medical record at YNHH; one will be made for your visit. Some information related to the care given to you during this visit will become part of your Yale New Haven Hospital (YNHH) medical record. For example, any laboratory test results that are sent to the YNHH lab for testing will appear in your medical record and any printed copies of your record. In addition, you need to know that when any person is admitted to the YNHH, the individual's previous medical records of other visits or admissions to YNHH become available to physicians and hospital staff in order to ensure that the best possible care can be provided to the individual during the hospital stay. Similarly, the researchers and staff will have access to whatever information is already in your YNHH medical records such as past surgeries or medical conditions, emergency room visits, or possibly clinic visits. If such access to your past medical history by researchers and staff responsible for the study is unacceptable to you, then you should not participate in the research study.

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When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, date of birth, address and phone number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential.

All identifiable information that is obtained in connection with this study is stored in password protected secure computer data files, and will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. All of the information obtained in this study is kept in locked files and will be kept confidential. When the study is completed subject information is stored at least for 7 years in locked cabinets within a locked storage unit that only the investigators of the study have access to. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 7 years, after which time the link will be destroyed and the data will become anonymous.

Information about your study participation will be entered into your Electronic Medical Record (EMR) in Oncore and EPIC. Once placed in the EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g., health insurance company, disability provider.)

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about [the new drug product or device] involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator: Dr. Renata Belfort de Aguiar
- The study sponsor: NIH/NIDDK
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators

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- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study
- Bank of America

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Authorized representatives of the National Institutes of Health and the FDA may need to review records of individual subjects. People from the FDA or other Health and Human Services agencies may see your name, but they are bound by rules of confidentiality not to reveal your child's identity to others.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, by deciding to take part in a double blinded treatment study and sign this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States

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federal or state government agency sponsoring the project that is needed for auditing or program evaluation by NIH/NIDDK which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctors as soon as you are able.

Yale School of Medicine and Yale-New Haven Hospital, do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the Study:

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments

The researchers may withdraw you from participating in the research if necessary. For example, you may be asked to withdrawal from the study if you are found to have a metal object in your body, or have a metal object placed in your body while you are enrolled in the study, if you experience significant discomfort during the procedures, are not able to follow instructions during

the procedures, or are not compliant with scheduled appointments. The researchers may also withdraw you from the study if you are not able to tolerate the study drug and it is making you feel sick.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

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Withdrawing Your Authorization to Use and Disclose Your Health Information:

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to;

Renata Belfort de Aguiar, M.D.
Yale University School of Medicine
300 Cedar street, TAC -S135
PO Box 208020
New Haven, CT 06520

If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

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Contact for Future Studies

We ask for your permission to contact you for participation in future studies that our group may conduct. We may use your telephone number, your email address or your physical address to contact you.

I agree to be contacted regarding future studies I may qualify for: (initial your choice)

_____YES _____No

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____

Signature:_____

Date:_____

_____ _____

Signature of Person Obtaining Consent Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator: Dr. Renata Belfort de Aguiarat 203-737-6067 or sugarbrainlab@yale.edu.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

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