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Naltrexone and Hypoglycemia in Type 1 Diabetes

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Hypoglycemia unawareness is a limiting factor in the treatment of type 1 diabetes and is a very difficult problem to reverse. Using positron emission tomography (PET), Dunn et al have recently demonstrated that patients with type 1 diabetes and hypoglycemia unawareness display a brain activation pattern during hypoglycemia that resembles the activation pattern seen following the administration of an addictive substance such as cocaine (1). In this response, the amygdala and hypothalamic regions associated with stress were less activated and the ventral striatum region associated with motivation and the lateral orbitofrontal cortex region associated with reward were not activated as strongly during hypoglycemia in the unaware compared to the aware subjects. These observations raise the question of whether one reason hypoglycemia unawareness is so difficult to reverse is that it is rewarding and not perceived as a stress to the patient, much like the response an addict has to a drug upon which he has grown dependent. If so, therapies applied to the treatment of addictions might provide a novel approach to the treatment of hypoglycemia unawareness in type 1 diabetes. One such therapy could be the orally administered non-addicting opioid antagonist naltrexone that has been shown to be effective in the treatment of many addictions (2-4).

The long-term goal of this project is to test the hypothesis that naltrexone therapy in subjects with type 1 diabetes and hypoglycemia unawareness will:

- reduce the number of hypoglycemic events (defined as number of episodes of hypoglycemia that require the assistance of another to recognize/treat and as minutes during which blood glucose is < 70 mg/dl as measured by continuous glucose monitoring, both over a 7 day period),
- improve recognition of hypoglycemia during experimental conditions, and
- reduce activation in the ventral striatum and lateral orbitofrontal cortex and increase activation in the amygdala and hypothalamus during hypoglycemia.

In this application, we describe a pilot study to determine if this treatment is of any benefit in treating hypoglycemia unawareness and to collect the observations necessary to develop a full-scale clinical trial of sufficient power to address our hypothesis. Our specific aim is to perform a randomized double blind trial of four weeks of naltrexone or placebo therapy in twenty subjects with type 1 diabetes and hypoglycemia unawareness and compare the outcome measures collected before treatment with those collected at the end of the treatment period.

Background and significance

Hypoglycemia unawareness is a limiting factor in the treatment of type 1 diabetes. Lack of awareness of hypoglycemia increases the risk for severe hypoglycemia, coma, and death during insulin therapy (5) and fear of hypoglycemia may prevent patients from optimally controlling their blood sugars, thereby increasing their risk for the development of diabetes complications. Strict avoidance of hypoglycemia has been known to partially restore awareness of hypoglycemia (6), however it is very difficult to achieve. Using PET, Dunn et al (1) have reported an increase in glucose uptake (a measure of activation) in brain regions associated with motivation (ventral striatum) and reward perception (lateral orbitofrontal cortex) and decreased activation of stress related regions (amygdala) during hypoglycemia in hypoglycemia unaware subjects with type 1 diabetes relative to hypoglycemia aware subjects with type 1 diabetes. This activation pattern resembles that seen in response to substances with addictive potential (7, 8), raising the question of whether one of the reasons that hypoglycemia unawareness is so difficult to reverse is that it is rewarding and not perceived as a stress to the patient.

Naltrexone, which can be delivered orally, has been shown to be safe and efficacious in the treatment of various addictive disorders such as alcoholism (4), opiate addiction (2) and pathological gambling (3). The drug binds primarily to the μ opioid receptor and is believed to block the binding of beta-endorphins released from the nucleus accumbens and ventral tegmental areas upon exposure to an addicting drug like alcohol. This blockade in turn ultimately affects downstream activation in regions associated with reward and craving (9). Naltrexone is approved by the Food and Drug Administration for treatment of alcoholism at a dose of up to 50 mg a day for an indefinite period of time but has been used in higher doses to treat pathological gambling (10). Efficacy in reducing alcohol cravings increases with treatment periods longer than 60 days, but were reduced by approximately half after 30 days of treatment (4). The drug has a black box warning about hepatotoxicity at doses above 50 mg/day, but in otherwise healthy out-patients, doses up to 200 mg a day were well tolerated and associated with normal liver function tests for more than a year (11).

During hypoglycemia, intravenous administration of the μ opioid receptor antagonist naloxone enhances the epinephrine and cortisol secretory responses during hypoglycemia in both normal controls and in patients with type 1 diabetes (12). More recently, naloxone infusion during an episode of hypoglycemia prevented the development of hypoglycemia associated autonomic failure in normal controls (13). These observations suggest that a m opioid receptor antagonist might be of benefit in the treatment of hypoglycemia unawareness through a direct effect on cerebral glucose sensing and/or the coordinated counterregulatory response even if it does not prove to have an effect on the activation of centers involved in motivation and reward.

Preliminary Data

Our research group is very experienced in all aspects of the methodology required to complete this project. We have a long track record of successfully recruiting subjects to participate in complicated metabolic studies (14-19). In recent years, our work has focused on subjects with type 1 diabetes (20, 21), many with hypoglycemia unawareness, and we have developed a registry of such subjects interested in participating in future studies. We also are skilled in the performance of clinical trials, having participated in the ACCORD trial since 1999 (22).

Most relevant to this application is our experience performing hypoglycemic clamp studies while brain activation is studied using magnetic resonance techniques. In our laboratory, we have used continuous arterial spin labeling (CASL) to identify brain regions that are activated in response to insulin-induced hypoglycemia in healthy human subjects (23). Five men and five women (age 29 ± 10 yrs, BMI 23.3 ± 2.1 kg/m2, mean ± SD) participated in this study. CASL images were acquired at euglycemia (99±5 mg/dl) and again during hypoglycemia (52 ± 3 mg/d;) using 2D GE-EPI (labeling time=2500 ms, resolution =2x2x3mm, 100 label/control pairs). In whole brain analysis, increases in regional cerebral blood flow, a measure of neuronal activation, were noted during hypoglycemia relative to euglycemia bilaterally in the medial thalamus, anterior cingulate, and posterior cingulate using BrainVoyager software, as has also been demonstrated by Teves et al using PET (TEVES PNAS 2004). These increases coincided with the peak responses in counterregulatory hormones (glucagon = 110 ± 41 pg/ml, epinephrine = 519 ± 273 pg/ml, norepinephrine = 405 ±124 pg/ml), providing evidence that activation of these brain regions is involved in the counterregulatory response to hypoglycemia. Focused region of interest analysis of specific regions such as the hypothalamus or amygdala was not performed in this study, but will be performed in the proposed project.

Research Design and Methods:
This study will be a randomized double blind placebo controlled trial involving 20 subjects with type 1 diabetes and hypoglycemia unawareness. Since the time necessary for the effect of naltrexone on our outcome variables to washout after a treatment period is unknown, each subject will serve as their own control and differences between the changes in the outcome measures will be evaluated between groups. The study design is depicted in the figure below.

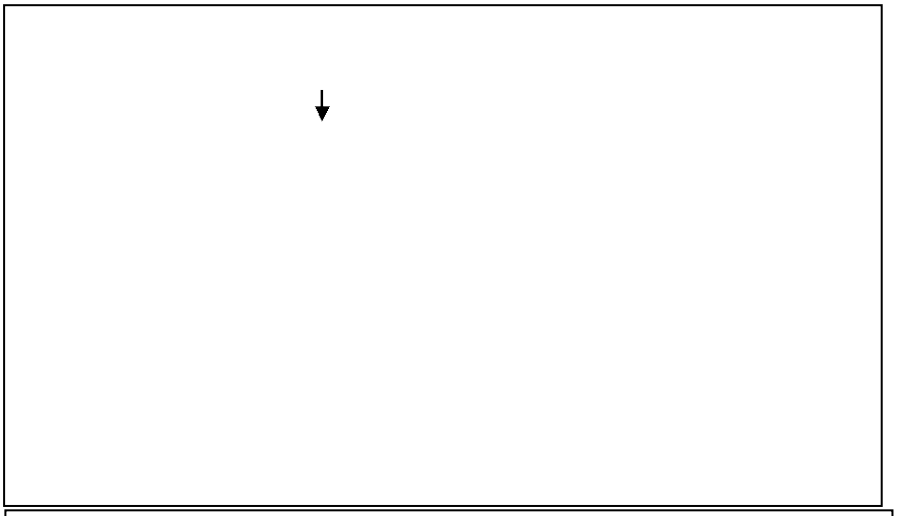
Subjects
Subjects between the ages 18 and 65 years of age will be recruited for participation from the University of Minnesota Endocrine Clinic and a registry of volunteers maintained by the investigators. Type 1 diabetes will be defined on clinical grounds. To be categorized as experiencing hypoglycemia unawareness, subjects must first report at the time of initial contact an inability to recognize at least some blood glucose values less than 50 mg/dl during the prior 3 months. At the time of the screening visit, subjects must then be defined as having hypoglycemia unawareness on a Cox questionnaire (24). Exclusion criteria will include concomitant use of acetaminophen, aspirin or ibuprofen (all may increase risk of naltrexone induced liver dysfunction), history of drug or alcohol abuse, current diagnosis or history of psychiatric illness, history of liver disease wiwth elevations in ALT/AST, history of renal insufficiency/failure (creatinine >1.5 mg/dL), pregnancy or breastfeeding, history of seizure or cardiac disease (both of which will increase risk of hypoglycemic clamp), history of stroke, head injury, or other chronic CNS disease, and presence of any characteristics that would preclude placement in the magnet (weight > 300 lbs, presence of metallic implants, etc.).

Experimental protocol
The screening visit will occur within two weeks of day zero, which will be the day of the first hypoglycemia study. At the screening visit, informed consent will be obtained and a standardized form will be used to insure subjects meet inclusion/exclusion criteria. Baseline labs for creatinine, ALT, AST, hemoglobin A1c, and CPK will be obtained. The subject will be educated in the use of the continuous glucose monitor and sent home with sufficient supplies to collect data for the seven days before the clamp study on day zero. During this period, subjects will also check their blood glucose before each of three meals and at bedtime and record the values as well as note any episodes in which another person was required to recognize and/or treat hypoglycemia. The continuous glucose monitor display will be blinded to the subject so that it does not influence their diabetes management.

Subjects will be admitted to the research center the afternoon before the hypoglycemic clamp study on day zero. They will be allowed to take their short acting insulin or a bolus via their pump with their evening meal, but their evening dose of long-acting insulin or their pump will be held after 6 PM. Blood glucose values will then be monitored every 1-2 hours and an intravenous infusion of insulin and/or glucose will be provided to maintain blood sugars between 100-150 mg/dl. Subjects will not be given additional food after their evening meal until the end of the hypoglycemic clamp on day zero.

On the morning of the study, subjects will be transferred to the Center for Magnetic Resonance Research. After their arrival, they will be prepared for clamp study by the placement of one intravenous catheter into one vein in each antecubital fossa for the later infusion of glucose, insulin, and potassium. A third intravenous catheter will be placed retrograde into a vein in the distal leg for later blood sampling. Baseline blood samples for glucose, glucagon, catecholamines, cortisol, and

growth hormone will then be collected no sooner than 30 minutes after catheter placement. At time 0 a constant infusion of insulin will be started at 2.0 mU/kg/min and the subject will be placed into the magnet. Plasma glucose be initially maintained at euglycemia (~100 mg/dl) while the baseline scan is done. Plasma glucose will than be reduced to 50 mg/dl and maintained at this level of glycemia for approximately thirty minutes. During the final 15 minutes subjects will be asked to quantitate their symptoms using a standardized method (25). Blood samples will be obtained every five minutes for measurement of plasma glucose concentration on a nearby analox machine and every twenty minutes for later measurement of glucagon, catecholamines, cortisol, and growth hormone.



Study design. CGMS= continuous glucose monitoring; BG=blood glucose; CASL = continuous arterial spin labeling; hypo= hypoglycemic; safety labs = ALT, AST, Cr, CPK

Cerebral blood flow will measured on a Siemens 3 Tesla magnet when the subject is euglycemic and again during the final 15 minutes of the hypoglycemic period. A T1 mapping technique will be used in which a RARE sequence with etl=8 echoes and an echo spacing of 7 ms with center-out k-space sampling (effective TE = 7 msec) is employed. CBF contrast will be achieved using FAIR (26)with a 12 msec long HS8 inversion pulse to generate a 6.6 Hz inversion bandwidth above a peak B1 of 500 Hz. A T1-image will be calculated at steady state from three acquired images on a pixel by pixel basis, as previously described (27).

Cerebral blood flow maps will be calculated according to:

$$CBF = \frac{\lambda}{T_1} \frac{S_0 - S_T}{S_T + (2\alpha - 1)S_0}$$

where λ (ml/g) denotes the brain-blood partition coefficient of water, T_1 (s) is the longitudinal relaxation time of tissue water, a is the efficiency of arterial spin labeling, and S_0 and S_T are signal intensities of control and arterial spin labeled images, respectively. Differences in whole brain cerebral blood flow measured during hypoglycemia and euglycemia will be determined for each subject. The perfusion images will then be transformed into Talairach space using the anatomic images and differences between individual regions of interest (such as amydgala, ventral striatum, lateral orbitofrontal cortex, and hypothalamus) during hypoglycemia and euglycemia will be determined for each subject. Dr. Silvia Mangia from the Center for Magnetic Resonance Research will be responsible for the collection and processing of the data collected using the 3 T magnet.

At the completion of the clamp study, subjects will be removed from the magnet, the insulin infusion will be discontinued,glucose will be given to achieve euglycemia, and subjects will be fed a meal. Randomization will then be done and subjects will be sent home with their assigned treatment. An

Investigational New Drug (IND) approval for the use of this medication for this study has already been obtained from the Food and Drug Administration. The investigational pharmacy at the University of Minnesota Medical Center will insure that the naltrexone and placebo tablets are identical in appearance and will maintain the log of the treatment assignment. Only the study pharmacist will have access to this log until the study is completed. The dose of the drug will be titrated up over 10 days (25 mg daily x 5 days, then 50 mg daily x 5 days, then 50 mg BID x 18 days). Subjects will be asked to avoid use of acetaminophen, non-steroidal anti-inflammatory medications and alcohol while taking naltrexone. At 14 ± 1 days, subjects will return to provide blood for measurement of ALT, AST, CPK, and creatinine. Drug will be stopped in subjects who experience an increase that exceeds two times the upper limit of normal for ALT, AST, or CPK or have a rise in their creatinine to 2.0 mg/dl or above in men or 1.5 mg/dl or above in women.

At the 14 day visit, subjects will be reminded to wear the continuous glucose monitor for the seven days before the next hypoglycemic clamp study and will be sent home with sufficient supplies to do so. On the night before the clamp study, they will be readmitted to the research center for preparation as outlined above. Repeat samples for ALT, AST, CPK, and creatinine will also be collected. On the day of the study, subjects will take their final dose of naltrexone/placebo and be transported to the Center for Magnetic Resonance Reserch to repeat the clamp study with measurement of cerebral blood flow described above.

Statistical analysis

This is a pilot study in which a sample size of 20 (10 subjects to receive placebo and 10 subjects to receive naltrexone) was arbitrarily selected to determine how large a sample size will be necessary to determine if naltrexone has an effect on our outcome measures. Each subject will serve as his/her own control and changes in the outcome variables (number of hypoglycemic events defined as number of episodes of hypoglycemia that require the assistance of another to recognize/treat and as minutes during which blood glucose is < 70 mg/dl as measured by continuous glucose monitoring, both over a 7 day period); symptom scores collected during hypoglycemia' and differences in regional blood flow noted between the euglycemic and hypoglycemic conditions for each study), will be compared between pre-treatment and end of treatment periods using Student's t-test with correction for repeated measures. Dr. Lynn Eberly from the Department of Biostatistics at the University of MInnesota will assist in the statistical analyses.

Anticipated problems/potential solutions

The most significant problem we may encounter is that our treatment outcomes will be unaffected by naltrexone treatment. Originally, we intended to focus on the effect of naltrexone on cerebral blood flow as a measure of regional activation during hypoglycemia, but since we are unaware of data that demonstrate naltrexone alters brain activation patterns in addicts, we have broadened our outcome measures to include more clinically relevant information such as frequency of hypoglycemia and symptom scores during controlled hypoglycemia. We are hopeful that naltrexone will have an effect on at least one of the outcome variables and will use the data collected from this pilot to design a larger study.

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