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Does an infusion of alpha-melanocyte stimulating hormone reduce blood sugar after a sugary drink in healthy people and those with type 1 diabetes mellitus?

Submission date
26/06/2020

Recruitment status
No longer recruiting

Registration date
02/07/2020

Overall study status
Completed

Last Edited
23/06/2023

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Current plain English summary as of 19/11/2021:
Background and study aims
Patients with type 1 diabetes and advanced type 2 diabetes commonly have high blood glucose levels after eating. This can injure body organs resulting in complications such as heart attacks, blindness and kidney failure. They require life-long treatment with the hormone insulin. While insulin therapy is effective it can come with significant side-effects like very low sugar levels (hypoglycaemia) and excessive weight gain. Researchers have discovered that a hormone from the brain called alpha melanocyte-stimulating hormone (α-MSH) reduces blood glucose in mice and sheep by making them more sensitive to insulin. Researchers now wish to find out for the first time if this is true in humans. They propose to infuse this hormone and measure blood glucose levels in healthy humans to determine whether α-MSH improves their insulin sensitivity.

Who can participate?
In parts one and two of the study, adults aged 18-50 who are healthy with no history of diabetes, who have had a stable body weight for at least 3 months and a BMI of ≥18 < 30 (i.e., not underweight or obese) will be eligible to take part. In part three the study will recruit adults aged 18-50 who have type 1 diabetes mellitus but are otherwise healthy, who have had a stable body weight for at least 3 months and a BMI of ≥18 < 30 (i.e., not underweight or obese).

What does the study involve?
There are three parts to the study.
In part one, healthy participants will attend four visits where they will receive an infusion of either α-MSH or saline (saltwater) at one of three concentrations. During the infusion, participants will have their glucose tolerance tested by drinking a cup of water with 75 g of sugar in it. Blood samples will be collected over this time (4 hours). Then participants will attend two visits where they will receive an infusion of either saline or α-MSH at the concentration found in part one to have the greatest effect on glucose tolerance. As well as the α-MSH infusion, they will also undergo a test that infuses insulin and glucose to very precisely measure

the effect of the α-MSH infusion on their insulin sensitivity. Over this time (6 hours) blood samples will be collected. Blood samples will be used to measure blood sugar, insulin, α-MSH, and gut hormones.
In part two, healthy participants will attend two visits where they will undergo glucose tolerance tests as described above while receiving an infusion of either high dose alpha-MSH or saline.
In part three, participants with type 1 diabetes mellitus attend two visits where they will undergo glucose tolerance tests as described above while receiving an infusion of either high dose alpha-MSH or saline.

What are the possible benefits and risks of participating?
There are no direct benefits to the participants medically. The risks are very low as the alpha-MSH peptide has been used in humans previously and has minimal side effects. Some facial flushing may occur for a few minutes, and potentially some nausea. A physician will be present during the infusion to manage these should they occur.

Where is the study run from?
Imperial College London (UK) and Ulster University (UK)

When is the study starting and how long is it expected to run for?
May 2019 to December 2024

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Brett Johnson
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Previous plain English summary:
Background and study aims
Patients with type 1 diabetes and advanced type 2 diabetes commonly have high blood glucose levels after eating. This can injure body organs resulting in complications such as heart attacks, blindness and kidney failure. They require life-long treatment with the hormone insulin. While insulin therapy is effective it can come with significant side-effects like very low sugar levels (hypoglycaemia) and excessive weight gain. Researchers have discovered that a hormone from the brain called alpha melanocyte-stimulating hormone (α-MSH) reduces blood glucose in mice and sheep by making them more sensitive to insulin. Researchers now wish to find out for the first time if this is true in humans. They propose to infuse this hormone and measure blood glucose levels in healthy humans to determine whether α-MSH improves their insulin sensitivity.

Who can participate?
Adults age 18-50 who are healthy with no history of diabetes, who have had a stable body weight for at least 3 months and a BMI of ≥18 < 30 (i.e., not underweight or obese)

What does the study involve?
There are two parts to the study. In part one participants will attend four visits where they will receive an infusion of either α-MSH or saline (saltwater) at one of three concentrations. During the infusion, participants will have their glucose tolerance tested by drinking a cup of water with 75 g of sugar in it. Blood samples will be collected over this time (4 hours).
In the second part of the study, participants will attend two visits where they will receive an infusion of either saline or α-MSH at the concentration found in part one to have the greatest effect on glucose tolerance. As well as the α-MSH infusion, they will also undergo a test that

infuses insulin and glucose to very precisely measure the effect of the α-MSH infusion on their insulin sensitivity. Over this time (6 hours) blood samples will be collected. Blood samples will be used to measure blood sugar, insulin, α-MSH, and gut hormones.

What are the possible benefits and risks of participating?
There are no direct benefits to the participants medically. The risks are very low as the alpha-MSH peptide has been used in humans previously and has minimal side effects. Some facial flushing may occur for a few minutes, and potentially some nausea. A physician will be present during the infusion to manage these should they occur.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
May 2019 to July 2022

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Brett Johnson
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Contact information

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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
275910

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 45135, IRAS 275910

Study information

Scientific Title
A physiological study of the effect of alpha-MSH on glucose clearance in healthy participants and those with type 1 diabetes mellitus

Acronym
Alpha-MSH

Study objectives
Current study hypothesis as of 19/11/2021:
Alpha-melanocyte stimulatory hormone (alpha-MSH) is a hormone that is produced by the brain and released into the bloodstream. It has multiple functions in the body, such as reducing inflammation, promoting skin pigmentation and controlling energy balance. It has recently been shown that in animals, infusion of alpha-MSH increases glucose clearance by promoting its uptake in skeletal muscle, thus lowering circulating blood sugar. Human studies to understand this action of alpha-MSH is a critical next step.

This study aims to observe the effect of alpha-MSH on increasing glucose clearance from the blood by promoting its uptake into skeletal muscle in healthy humans and those with type 1 diabetes mellitus

Hypothesis: Alpha-melanocyte stimulating hormone improves post-prandial glucose clearance versus saline in healthy humans and those with type 1 diabetes mellitus

Previous study hypothesis:
Alpha-melanocyte stimulatory hormone (alpha-MSH) is a hormone that is produced by the brain and released into the bloodstream. It has multiple functions in the body, such as reducing inflammation, promoting skin pigmentation and controlling energy balance. It has recently been shown that in animals, infusion of alpha-MSH increases glucose clearance by promoting its uptake in skeletal muscle, thus lowering circulating blood sugar. Human studies to understand this action of alpha-MSH is a critical next step.

This study aims to observe the effect of alpha-MSH on increasing glucose clearance from the blood by promoting its uptake into skeletal muscle in healthy humans.

Hypothesis: Alpha-melanocyte stimulating hormone improves post-prandial glucose clearance versus saline.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/05/2020, London - Fulham Research Ethic Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048235; fulham.rec@hra.nhs.uk), REC ref: 20/LO/0355

Study design
Randomised; Both; Design type: Not Specified, Not Specified, Cross-sectional

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Glucose clearance from the blood

Interventions

Current intervention as of 19/11/2021:
For this prospective double-blinded (both the researchers and study participants are unaware of the intervention) randomised control trial (RCT) the researchers plan to recruit 15 healthy volunteers from the general public for work package 1, 22 of the same for work package 2, and patients with type 1 diabetes mellitus for work package 3. The participants will be healthy male and female volunteers or those with type 1 diabetes mellitus above the age of 18 with no major medical conditions.

Prior to being accepted into the study, participants will first be screened by a member of the research team to ensure they meet the inclusion and exclusion criteria. At this screening visit, participants will be informed about the study and have the opportunity to ask questions. They will be given a detailed participant information sheet which they may keep to review. Once the participant has been given a minimum of 24 h to consider their entry into the study, informed consent in person will be obtained.

Work package 1:
This work package will be comprised of two sub-studies run sequentially, to find the most effective dose of alpha-MSH, and then to assess its effect on whole body insulin sensitivity.
We will conduct a prospective randomised double-blinded physiological study to recruit 15 healthy participants from either sex from the community. On each of these four study visits, participants will undergo an oral glucose tolerance test and will be randomized to either a placebo infusion or infusion of alpha-MSH, at one of three doses (15, 150, 1500 ng/kg/hr). Each participant will be studied at least 2 days apart in a randomized, double blind, placebo-controlled, crossover manner.
On completion of dose-finding, a euglycaemic hyperinsulinaemic clamp will be conducted with placebo and the dose of alpha-MSH observed to induce the maximal change in the area under the curve of glucose and/or insulin concentration during an OGTT, and as long as it does not cause hypoglycaemia. Each participant will be studied at least 2 days apart in a randomized, double- blinded, placebo-controlled, crossover manner.

Work package 2:
Participants will undergo two OGTT visits, at least 2 days apart, during which they will be randomised to receive either saline or 1500 ng/kg/hr alpha-MSH.

Work package 3:
Participants will undergo two OGTT visits, at least 2 days apart, during which they will be randomised to receive either saline or 1500 ng/kg/hr alpha-MSH.

The blood collected throughout the infusions will be analysed in the lab for relevant hormones and proteins.

Previous intervention:
For this prospective double-blinded (both the researchers and study participants are unaware of the intervention) randomised control trial (RCT) the researchers plan to recruit 15 healthy volunteers from the general public. The participants will be healthy male and female volunteers (we aim to recruit 8 males and 7 females) above the age of 18 with no major medical conditions.

Prior to being accepted into the study, participants will first be screened by a member of the research team to ensure they meet the inclusion and exclusion criteria. At this screening visit, participants will be informed about the study and have the opportunity to ask questions. They will be given a detailed participant information sheet which they may keep to review. Once the

participant has been given a minimum of 24 hours to consider their entry into the study, informed consent in person will be obtained.

Every participant will then attend 4 separate morning visits at Hammersmith Hospital after an overnight fast (fasted since 10 pm the night before). Each visit will last approximately 4 hours and take place at a minimum of 1-week intervals. At each of these visits the participants will be randomised (assigned at random by a computer programme) to infusions of one of three doses of alpha-MSH or placebo (normal saline - 0.9% sodium chloride (salt) solution). These infusions will last for 150 minutes and will be delivered through an intravenous cannula placed in the arm. A second cannula will be inserted into the other arm to enable extraction of blood samples. Thirty minutes after each infusion begins, participants will be asked to consume a sugary drink which will raise their blood sugar levels. Throughout the infusion, blood will be drawn and circulating blood glucose measured. This will allow the researchers to measure the body's response to glucose under each of the doses and compare this to the placebo in order to identify the dose at which alpha-MSH acts to reduce blood sugar.

Once all participants have completed four infusion visits (three doses of alpha-MSH and one placebo visit) with oral glucose tolerance tests, they will be invited back for a further two morning fasted visits at Hammersmith Hospital. Each visit will last approximately 4 hours, during which participants will undergo what is known as a 'glucose clamp' where their blood glucose is maintained at a stable level during an infusion of insulin with alpha-MSH or placebo. The participant will require three separate intravenous lines (one for insulin, one for either alpha MSH or placebo and one for extracting blood samples). During one of these visits, the dose of alpha-MSH administered will be that which is observed to cause the greatest change in blood glucose levels during the glucose tolerance test visits. In the other visit, saline will be administered as placebo. At the first of these two visits, the participant will be randomised to alpha-MSH or placebo, with the second visit administering the infusion not given in the first. Both the researchers and participant will be unaware of the treatment during these visits. This glucose clamp technique will allow the researchers to quantify the amount of glucose that is being used by the body in response to an infusion of alpha-MSH. The study will conclude when participants complete two glucose clamp visits.

If any of the expected side effects (nausea, facial flushing, general discomfort) are present at any dose they will be assessed via the Visual Analogue Scale provided, where the participant will rate each sensation by marking with a dash along a 10 cm line.

The blood collected throughout the infusions will be analysed in the lab for relevant hormones and proteins.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Alpha-MSH

Primary outcome measure
Current primary outcome measure as of 19/11/2021:
Work Package 1:

1. Difference in the total or incremental area under the curve of glucose concentration at an OGTT during saline vs. alpha-MSH infusion at 0-180 minutes
2. Difference in the total or incremental area under the curve of insulin concentration at an OGTT during saline vs. alpha-MSH infusion at 0-180 minutes
3. Difference in the glucose infusion rate at the euglycaemic hyperinsulinaemic clamp during saline vs. alpha-MSH infusion
Work Package 2:
1. Difference in the total or incremental area under the curve of glucose concentration at an OGTT during saline vs. 1500 ng/kg/hr alpha-MSH infusion at 0-180 minutes
2. Difference in the total or incremental area under the curve of insulin concentration at an OGTT during saline vs. 1500 ng/kg/hr alpha-MSH infusion at 0-180 minutes
Work Package 3:
1. Difference in the total or incremental area under the curve of glucose concentration at an OGTT during saline vs. 1500 ng/kg/hr alpha-MSH infusion at 0-180 minutes

Previous primary outcome measure:
1. Area under the curve of glucose concentration measured using blood tests at an OGTT during saline vs. alpha-MSH infusion visits at 0-180 minutes
2. Glucose infusion rate measured using blood tests at the euglycaemic hyperinsulinaemic clamp during saline vs. alpha-MSH infusion visits at 0-240 minutes

Secondary outcome measures

Current secondary outcome measures as of 19/11/2021:
Work Package 1:
1. Difference in the total or incremental area under the curve of the concentration of the following metabolites during OGTT and clamp with saline or alpha-MSH infusion at 0-180 minutes:
1.1. Insulin measured using blood tests
1.2. C-peptide measured using blood tests
1.3. Glucagon measured using blood tests
1.4. GLP-1 measured using blood tests
1.5. α-MSH measured using blood tests
2. Adverse events (including flushing) as reported by the participant using visual analogue scales at -30 to 180 minutes
Work Package 2:
1. Difference in the total or incremental area under the curve of the concentration of the following metabolites during OGTT and clamp with saline or 1500 ng/kg/hr alpha-MSH infusion at 0-180 minutes:
1.1. Insulin measured using blood tests
1.2. C-peptide measured using blood tests
1.3. Glucagon measured using blood tests
1.4. GLP-1 measured using blood tests
1.5. α-MSH measured using blood tests
2. Adverse events (including flushing) as reported by the participant using visual analogue scales at -30 to 180 minutes
Work Package 3:
1. Difference in the total or incremental area under the curve of the concentration of the following metabolites during OGTT and clamp with saline or 1500 ng/kg/hr alpha-MSH infusion at 0-180 minutes:
1.1. Insulin measured using blood tests
1.2. C-peptide measured using blood tests

1.3. Glucagon measured using blood tests
1.4. GLP-1 measured using blood tests
1.5. α-MSH measured using blood tests
2. Adverse events (including flushing) as reported by the participant using visual analogue scales at -30 to 180 minutes

Previous secondary outcome measures:
1. Area under the curve for the following metabolites during OGTT and clamp during saline or alpha-MSH infusion visits at 0-180 minutes:
1.1. Insulin measured using blood tests
1.2. C-peptide measured using blood tests
1.3. Glucagon measured using blood tests
1.4. GLP-1 measured using blood tests
1.5. α-MSH measured using blood tests
2. Adverse events (including flushing) as reported by the participant using visual analogue scales at -30 to 180 minutes

Overall study start date
05/05/2019

Completion date
31/12/2024

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 19/11/2021:
Work Package 1 and 2:
1. 18-50 years old
2. Normal fasting glucose (< 5.6 mmol/l)
3. Stable body weight for at least 3 months
4. BMI ≥18 and <30 kg/m²
5. The participant is capable of giving written informed consent
6. The participant is able to read, comprehend and record information written in English

Work Package 3:
1. 18-50 years old
2. Diagnosis of T1DM with low/undetectable plasma C-peptide
3. Stable body weight for at least 3 months
4. BMI ≥18 and <30 kg/m²
5. The participant is capable of giving written informed consent
6. The participant is able to read, comprehend and record information written in English

Previous participant inclusion criteria:
1. 18-50 years old
2. Normal fasting glucose (< 5.6 mmol/l)
3. Stable body weight for at least 3 months
4. BMI > = 18 < 30 kg/m²
5. The participant is capable of giving written informed consent
6. The participant is able to read, comprehend and record information written in English

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
Both

Target number of participants
59

Key exclusion criteria
1. Previous or current psychiatric diagnosis listed in DSM-V Axis 1
2. Significant current or past medical or psychiatric history that, in the opinion of the investigators, contraindicates their participation
3. History of type 1 or type 2 diabetes mellitus
4. History of endocrine disorder
5. History of ischaemic heart disease, hypertension, heart failure, cardiac arrhythmia, peripheral vascular or cerebrovascular disease.
6. History or presence of significant respiratory, gastrointestinal, hepatic, oncological, neurological or renal disease or other condition that in the opinion of the Investigators may affect participant safety or outcome measures
7. Unwillingness or inability to follow the procedures outlined in the protocol
8. History of sensitivity to any of the peptides, or components thereof, or a history of drug or other allergy that, in the opinion of the investigators, contraindicates their participation
9. Use of current regular prescription or over-the-counter medications that in the opinion of the Investigators may affect participant safety or outcome measures
10. Clinically significant abnormalities in screening electrocardiogram (ECG) or blood tests abnormalities which in the opinion of the study physician, is clinically significant and represents a safety risk
11. Current pregnancy or breast-feeding in female participants (the Investigators would advise on using contraception for the duration of the visits)
12. Pulse rate < 40 or > 100 beats per minute OR systolic blood pressure > 160 and < 100 and a diastolic blood pressure > 95 and < 50 in the semi-supine position
13. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first experimental visit in the current study: 90 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)
14. Exposure to more than 3 new investigational medicinal products within 12 months prior to the screening
15. Participants who have donated, or intend to donate, blood within three months before the screening visit or following study visit completion

Date of first enrolment

15/09/2020

Date of final enrolment
31/10/2024

Locations

Countries of recruitment
England

Northern Ireland

United Kingdom

Study participating centre
Imperial College Healthcare NHS Trust
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Study participating centre
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Study participating centre
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Sponsor type
University/education

Website
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ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal. No additional files currently available.

Intention to publish date
31/12/2023

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No