CHIEF SCIENTIST OFFICE

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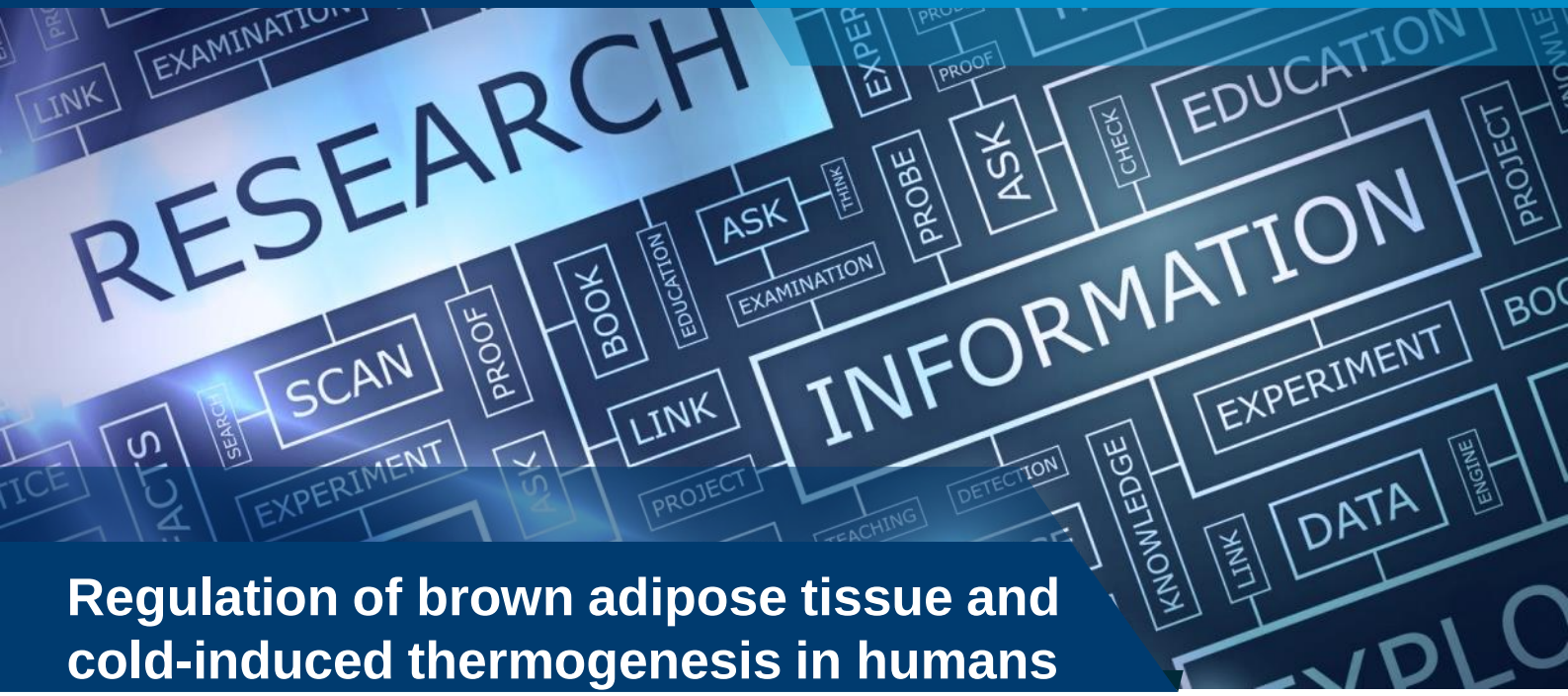
RESEARCH PROJECT BRIEFING



Regulation of brown adipose tissue and cold-induced thermogenesis in humans

AIMS

Brown adipose tissue (BAT) or brown fat is a special type of fat that generates heat to keep our bodies warm when we're in a cold environment, this process is called cold-induced thermogenesis. Activating brown fat is a possible strategy to treat obesity and its associated diseases, by increasing the energy we burn to help people lose weight. In this fellowship our main aims were to determine if brown fat function is abnormal in obesity, and identify new pathways that control brown fat thermogenesis in humans.

KEY FINDINGS

- We determined that the amount of uncoupling protein 1 (the protein that is responsible for generating heat in brown fat during thermogenesis) in human brown fat is reduced in older people with obesity, and in those with risk factors for developing heart disease such as high blood pressure and diabetes.
- We determined that people with obesity under the age of 40 have comparable brown fat function to people of normal weight, while older people still retain specialised cells in their body (called precursor cells) with the capacity to turn into new brown fat cells.
- We identified that serotonin binds to receptors on the outside of brown fat cells which reduces brown fat function, and that the serotonin transporter is present on human brown fat cells which enhances brown fat function by 'eating up' and destroying the serotonin.
- We showed the inhibitors of the serotonin transporter called selective serotonin reuptake inhibitors or SSRIs, these are the most commonly prescribed medications to treat depression, reduce brown fat function, potentially revealing a new mechanism through which SSRIs may cause weight gain and diabetes.
- We identified a new way of detecting brown fat in humans using a special technique called positron emission tomography using a specially labelled form of a molecule called choline.

WHAT DID THE STUDY INVOLVE?

In this work we used two complementary approaches to investigate human brown fat function:

1) We obtained brown fat (which is found in several parts of the body but is most abundant in the neck) and white fat (the typical fat we think of in the body) from patients undergoing surgery in the neck. We either froze this tissue for analysis or used the tissue to grow brown and white fat cells that we could then study. We measured the abundance of different genes in these tissues (such as uncoupling protein 1) to identify how brown fat function is controlled differently to white fat. We also treated brown fat cells with various drugs (e.g. serotonin or SSRIs) or removed some of the genes in these cells to work out how they altered brown fat function.
2) We recruited healthy volunteers (6-16 per study) to different studies investigating brown fat function. We exposed these volunteers to mild cold (~16°C) and measured how much energy they burned, and measured their brown fat function using special scans of the body called positron emission tomography (PET) using radioactive tracers such as glucose and measured their skin temperature using heat-sensitive cameras. These volunteers were sometimes given medications (e.g. the SSRI sertraline) on one visit and dummy placebo tablets on another so we could find out how these medications altered brown fat function.
3) As these studies involved cold exposure, we involved healthy volunteers from our previous studies to help us design acceptable protocols for the current fellowship. Specifically, we were keen to determine what level of cold and the number of procedures were acceptable to participants. The volunteers we recruited to the studies in this fellowship were obviously critical for the successful execution of the project and they have also helped us guide potential future treatment strategies.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

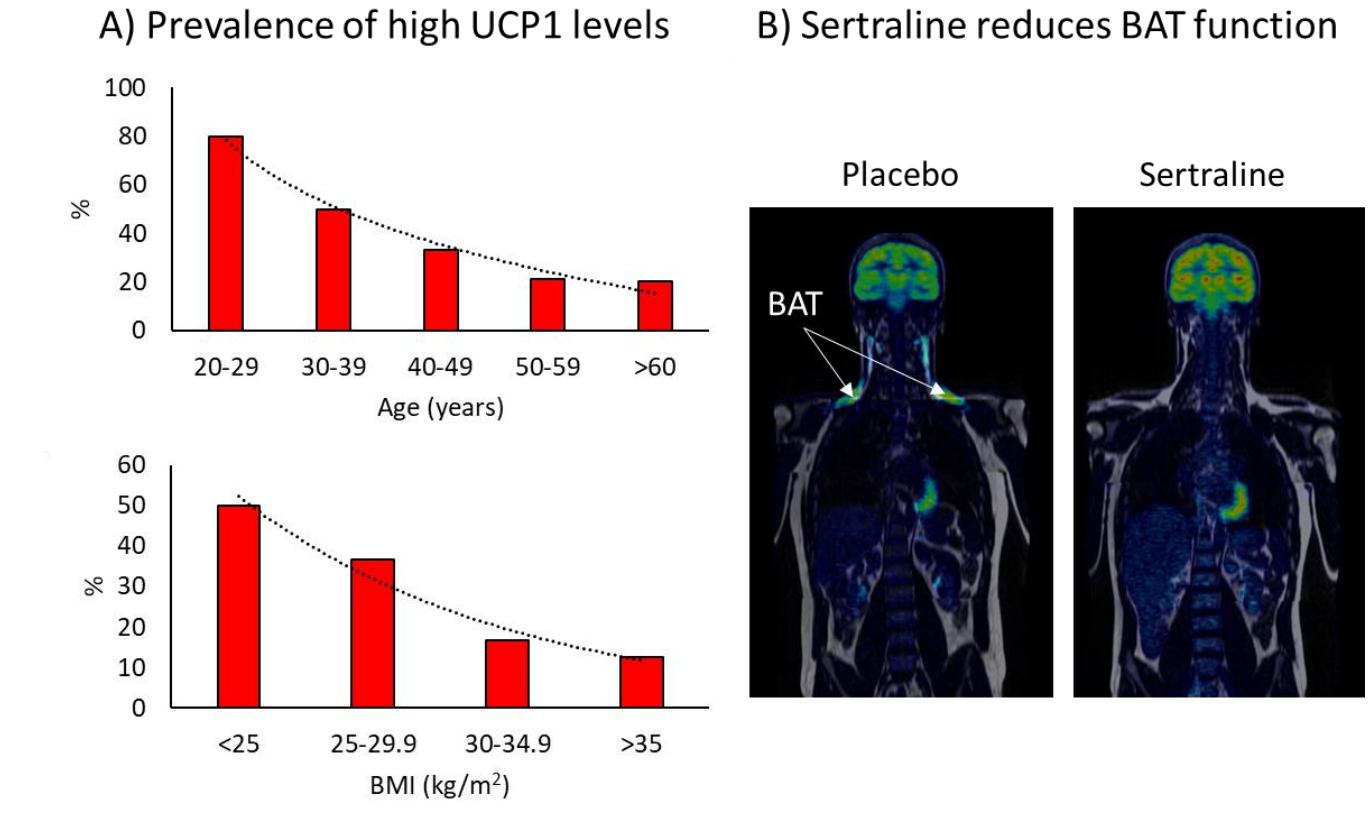
1) Study 1 – We obtained brown and white fat samples from ~140 patients and measured the abundance of uncoupling protein 1 (UCP1, the key protein that produces the heat by brown fat) in either whole tissue (~55) or in precursor fat cells (~85) which we cultured outside the body and turned into new fat cells. The amount of UCP1 in brown but not white fat decreased with increasing age, fat mass (Figure 1A), fasting glucose and insulin, and blood pressure in whole tissue. However, even older and obese patients had precursor cells that we were able to turn into new brown fat cells, these cells had comparable UCP1 levels to those from younger normal weight individuals. These results demonstrated that human brown fat function declines with age, obesity and cardiometabolic risk factors, but that new precursor cells are still present in these people that can form new brown fat cells at least in culture, we are now investigating how to make people grow more brown fat in their bodies.

2) Study 2 – In study 1, we noted that UCP1 levels were similar in normal weight and obese patients aged under 40 years, so undertook a study in 12 young adult healthy volunteers (6 normal weight and 6 age-matched obese). These people were placed in a cold room at ~16 °C for 2 hours and we undertook PET scanning using a radioactive glucose tracer to measure brown fat function. We demonstrated that brown fat mass and activity was preserved in these young adults with obesity, revealing the use of specific medications to activate brown fat at room temperature may be a viable therapeutic strategy in this group.

3) Study 3 – We measured all the genes in human brown and white adipocytes to try and identify new pathways that control brown fat function. Through this we identified a key role for the serotonin transporter in brown fat. We determined that serotonin binds to the surface of brown fat cells and reduces its heat production, and that the transporter 'sucks up' and removes this serotonin to maintain normal brown fat function. Selective serotonin reuptake inhibitors (SSRIs) are the most common class of drug used to treat depression and these drugs work by inhibiting the serotonin transporter, these medications cause weight gain and diabetes but the mechanism is unclear. We then recruited 15 healthy volunteers to a study and gave them an SSRI or dummy placebo in random order and found that the SSRI reduced their brown fat function (Figure 1B). These data reveal a new mechanism that may contribute to the weight gain and diabetes seen with SSRI use. We also published the genes we identified in human brown fat to allow other researchers to use this dataset for their future research.

4) Study 4 – Finally, we determined that human brown fat can be identified without the need for cooling patients by pioneering PET scanning with a specially labelled form of a nutrient called choline in healthy volunteers, usually labelled glucose (a sugar) is used but requires the patient to be cold to detect the brown fat. Choline is important for normal cell function and we have since found that it is used for making different types of fats in human brown fat. This research has shown how developing new techniques can improve our understanding of human brown fat function.

Figure 1- Regulation of human brown adipose tissue (BAT) function.
A) Data depict the percentage of patients with high UCP1 levels in BAT, which decreased substantially with increasing age (top panel) and body mass index (BMI) (lower panel). B) Representative PET images from a healthy volunteer given either placebo (left) or the SSRI sertraline for 7 days. There was substantial glucose uptake by BAT, a measure of brown fat activation, during cold exposure on the placebo phase (white arrows), which was blocked by sertraline.



WHAT IMPACT COULD THE FINDINGS HAVE?

- This research has highlighted the potential importance of activating brown adipose tissue as a novel treatment for obesity and prevent the metabolic consequences of obesity.
- We are now testing the effect of specific medications that target pathways identified in this research fellowship, in humans with obesity to see if this will increase brown fat activity and improve wider metabolic health, this may reveal a new approach to treat these patients.
- The novel datasets we identified and have published will allow researchers to identify further novel pathways which may lead to other new therapeutic strategies.

HOW WILL THE OUTCOMES BE DISSEMINATED?

The outcomes will be disseminated by publication of the original research articles (e.g. Suchacki KJ *et al*, Nature Metabolism 2023; https://www.nature.com/articles/s42255-023-00839-2) and presentations at national/ international conferences by the PI and other members of the team (https://www.ese-hormones.org/what-we-do/awards/ese-awards/european-journal-of-endocrinology-award/previous-winners/). These outputs will and have been disseminated through public engagement opportunities (e.g. recent Edinburgh and Falkirk Science festivals).

This fellowship has led on to new projects researching how brown fat is beneficial for metabolic health, how we can grow more brown fat and testing the effect of medications to activate brown fat in humans. Finally, this fellowship has been important in the training of 2 PhD students, who are both due to defend their theses in the near future.

CONCLUSION

We conclude that this fellowship has provided evidence that brown fat function is reduced in older obese adults and in those with obesity-related complications such as high blood pressure and diabetes. We have identified entirely novel pathways regulating human brown fat function that may lead to new therapeutic approaches to treat obesity and associated cardiometabolic disease.

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Additional Information

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