Home Office

NON-TECHNICAL SUMMARY

Effects of changes in blood glucose on brain and the central control of metabolism

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
    - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.
    - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.

Key words

Diabetes, Glucose, Hypoglycaemia

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is required, and should be submitted within 6 months of the licence's revocation date.

Reason for retrospective assessment

This may include reasons from previous versions of this licence.

- Contains severe procedures
- Required at inspector's discretion

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

Diabetes is a common and growing group of conditions in which blood sugar (glucose) levels rise. It can result in serious medical problems- blindness, kidney failure, gangrene and amputation, heart attacks and early death.

Normally, the body controls blood sugar by producing a protein called insulin from specialised cells in the pancreas. In diabetes, the body fails to produce enough insulin levels to keep blood sugar in check.

Many people with diabetes have to inject themselves several times daily with insulin to keep blood glucose (sugar) controlled. Sometimes their blood sugar may drop too low- for example if they eat less or misjudge the amount of insulin needed. This is called hypoglycaemia (or a "hypo"). Most people notice a falling blood sugar as it results in symptoms such as hunger, shaking or confusion. As many as 1 in 5 people with insulin treated diabetes don't get these symptoms early enough to stop them from falling into a deep hypo with drowsiness, lethargy and eventually even resulting in unconsciousness.

In this project, we aim to find out how the body recognises a low blood sugar, how the symptoms (and other responses to a low blood sugar) are created and why these may change in diabetes.

A retrospective assessment of these aims will be due by 16 June 2024

The PPL holder will be required to disclose:

- Is there a plan for this work to continue under another licence?
- Did the project achieve it's aims and if not, why not?

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

The information gained in this work may:
(1) help us to identify people with diabetes at higher risk of losing the ability to notice hypos. To do this, we are working with colleagues across Europe looking at large databases from clinical studies of diabetes.
(2) identify brain pathways responsible for protecting against a hypo and how these can change in diabetes. This may then allow new treatments – for example a medicine which could act on these brain areas- to be designed to boost the awareness of a hypo.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

We will use up to 5500 mice (of all ages) over 5 years.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

Most mice in the project will be used for breeding.

Some mice will be made diabetic (either by changing their diet to a high fat diet to mimic an unhealthy western diet and/or injecting a chemical which destroys the insulin producing cells in the pancreas). Like humans with diabetes, some of these may need regular insulin treatment. This may either be by daily injections or by having a slow release insulin pellet inserted under the skin (under anaesthesia). Also like humans with diabetes, they may need to have regular blood tests to monitor blood sugar. We may deliberately create hypos to simulate and measure what happens in humans with diabetes.

Some mice may undergo surgery under anaesthesia to have catheters (indwelling tubes) implanted into blood vessels to allow us to take blood samples without the need for repeated piercing of the skin with needles and/or test their responses to insulin and sugar infusions (a slow drip delivered into the blood stream through a catheter). We will measure blood sugar and other changes in blood such as levels of adrenaline (a marker of stress and an important defensive response to low blood sugar).

This surgery is difficult and we expect that this will be unsuccessful on occasions. Where this is apparent during the surgery, mice will be killed while still anaesthetised. We will also monitor mice very carefully in the first 60 minutes after surgery and if not recovering, will be killed. Although this strategy will minimise suffering, some mice (we expect less than 5% undergoing the most challenging surgery where we insert catheters into the main carotid artery in the neck) may die unexpectedly in the days after surgery before the end of studies.

We may also monitor how hungry mice are, whether they notice that their blood sugar is low and how quickly and accurately they can complete computerised tasks. To do this, we will train them to respond- for example by pressing a button to receive a milkshake treat.

Because special sugar-sensing areas deep within brain are an important part of the way in which sugar is detected, some mice may also have brain surgery to inject special virus treatments which then allow us to use chemicals to stimulate sugar-sensing cells deep inside brain.

At the end of studies, mice will be killed.

A retrospective assessment of these predicted harms will be due by 16 June 2024

The PPL holder will be required to disclose:

- What harms were caused to the animals, how severe were those harms and how many animals were affected?

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

The sugar-sensing cells that we are interested in studying are located deep within brain. They are too small to be seen with current brain imaging methods in humans.

Studying sugar sensing cells outside the body (for example grown in test tubes or flasks) can replace partly animal work. Typically, this has involved using a type of tumour cell which can be grown in the laboratory and appears to be sugar sensing. We don't know though how closely this matches the sugar (and specifically hypo) sensing cells in brain. Other scientists have used human brain cells obtained through tissue banks.

We liaise with these scientists and also have colleagues locally who are working to try and make stems cells grow into human brain cells in the laboratory. Although exciting, all of these approaches are still at an early stage. A further current limitation is that we need to know how groups of cells (rather than individual cells) work together as part of the whole-body response to a low sugar level.

We continue to watch these areas carefully though and as they develop, these may allow us to replace partly or fully the need for animal work.

We also considered carefully what type of animals to use in this work. There are 2 reasons for using mice in this work. Firstly, we already have data suggesting that many aspects of blood glucose control are similar to humans. Secondly, a number of different "genetic" models exist, often with very small changes in specific cell types in the body. This means that we can study how these genetic differences/ specific cells work to maintain blood glucose levels.

A retrospective assessment of replacement will be due by 16 June 2024

The PPL holder will be required to disclose:

- What, if any, non-animal alternatives were used or explored after the project started, and is there anything others can learn from your experience?

Reduction

Explain how you will assure the use of minimum numbers of animals.

We will ensure careful and scrupulous design of studies to make them as efficient as possible (finding out what we need to do with the minimum number of mice).

As part of this, we will try to get as much information as possible from each and every mouse, particularly those undergoing the studies needing surgery. To do this, mice may receive a blood transfusion from littermates (killed by deep anaesthesia for blood collection) to allow us to collect enough blood to study mice in depth and on more than 1 study day.

At the end of studies, when mice are killed, we will save and store as many tissue samples from mice as possible. This may allow us to answer future questions without the need for fresh experiments on more mice.

We will also make certain that we are up to date with the science in this area so that we are not duplicating work that has already been performed elsewhere.

A retrospective assessment of reduction will be due by by 16 June 2024

The PPL holder will be required to disclose:

- How did you minimise the numbers of animals used on your project and is there anything others can learn from your experience?

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

Just as for humans, surgery in mice can be painful for a few days and surgical wounds can become infected. Mice undergoing surgery in this programme of work will have painkillers and sometimes antibiotics. They will be monitored closely especially in the time immediately after surgery to ensure complete recovery and welfare.

We aim to make certain that day to day handling of mice is as stress free as possible. Mice prefer to be in company of other mice rather than alone in cages. We are looking at whether we can change the way in which we perform surgery to allow this by using metallic caps or protective jackets/ coverings over surgery sites to prevent mice from chewing.

We will also look at whether we can use implanted glucose sensors (similar to those used in human diabetes) to allow continuous remote monitoring of blood sugar in mice with diabetes without the need for such frequent blood tests

A retrospective assessment of refinement will be due by by 16 June 2024

The PPL holder will be required to disclose:

- With the knowledge you have now, could the choice of animals or model(s) used be improved for future work of this kind? During the project, how did you minimise harm to the animals?