Home Office

NON-TECHNICAL SUMMARY

Metabolic sensing and energy homeostasis

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

Obesity, metabolic diseases, brain, neurocircuits

Retrospective assessment

> The Secretary of State has determined that a retrospective assessment of this licence is not required.

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?

Obesity is a disease of brain pathways regulating appetite. These pathways rely on sensing mechanisms to detect how much energy is available in the body and what kind of nutrients are available for biological functions. Brain nutrient and energy sensing pathways are poorly characterized, which hinders our ability to develop safe and efficient drugs to prevent and treat obesity. In this project, we want to characterize brain pathways sensing proteins that are important in the regulation of energy balance and understand the role of various brain cell types , including immune cells, in these processes. We know that dietary proteins promote satiety and leanness, but how the brain detects proteins and how this detection modulates hunger and satiety is poorly understood. Characterizing these pathways will increase our knowledge of brain pathways regulating appetite and metabolism and may lead to the discovery of new research avenues to develop safe and efficient drugs in the treatment of obesity and associated metabolic diseases.

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?

Obesity represents a major threat to public health, as it is a major risk factor for premature mortality from cardiovascular diseases and certain cancers. The direct costs of treating overweight and obese people are constantly increasing (£4.2 billion in 2007) while indirect costs reached £27 billion in 2015. There is currently no safe and efficient drug therapy to prevent or treat obesity. The aim of this project is to understand how the brain senses proteins and how this sensing regulates appetite to identify new research avenues for safe and efficient anti-obesity drugs. Direct benefits that will likely arise from this work: increased knowledge and understanding of how the brain senses proteins. These findings will be used by our group and other researchers to further study the biology of brain protein sensing. We will also identify how brain pathways sensing proteins interact with brain pathways sensing energy and other nutrients, to determine if targeting distinct brain pathways in combination could produce greater health benefits. Last, we will determine how brain protein sensing produce a coordinated regulation of appetite and metabolism, to better understand how the body fights against weight loss during chronic energy restriction. Indirect medium-term benefit: Our findings will lay the foundation for follow-up preclinical and clinical research. They will identify candidate therapies directly targeting brain protein sensing mechanisms, pathways integrating protein and energy sensing, and pathways coupling energy expenditure and appetite. We will collaborate with our colleagues at the IMS studying the genetics of obesity in Humans to see if the pathways and genes we have identified are associated with obesity or metabolic diseases in the human population. In the long-term, our findings may contribute to the development of efficient treatments for human obesity.

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?

I expect to use around 9000 wild-type and transgenic mice 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?

The majority of animals (90%) are not expected to show signs of adverse effects that impact materially on their general well-being, and may transiently show moderate clinical signs (piloerection, reduced activity). Very rarely the severity of these signs may be such that the humane end points may be reached. Animals are monitored on a regular basis to detect any sign of distress or suffering. Analgesic agents will be administered as required. At the end, all animals will be killed.

Replacement

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

We need to use whole organisms because the control of energy balance and metabolism occurs at the level of the “whole organism” and not simply at a cellular level. We need to use mammals to model how the human brain works because mammals have unique sophisticated pathways to regulate feeding and metabolism. However, we have developed and continue the development and use of primary cell culture, immortalized cell lines and brain explants to model primary sensing mechanisms and intracellular signalling pathways in vitro.

Reduction

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

We need to use whole organisms because the control of energy balance and metabolism occurs at the level of the “whole organism” and not simply at a cellular level. We need to use mammals to model how the human brain works because mammals have unique sophisticated pathways to regulate feeding and metabolism. However, we have developed and continue the development and use of primary cell culture, immortalized cell lines and brain explants to model primary sensing mechanisms and intracellular signalling pathways in vitro.

As often as possible. We will request tissues from collaborators and perform measurements on shared tissues.

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.

Rodents allow the study of whole body control of energy balance in a manner relevant to humans, as pathways involved in the control of appetite and body weight are largely similar between rodents and humans. Rodents allow access to several tissues critical to the control of metabolism (brain, pancreas) that are inaccessible in humans. Rodents are amenable to genetic manipulations, offering endless possibilities to characterize mechanisms underlying diseases in a specific and relevant manner.

We will take a number of measures to refine our use of rodents and minimize welfare costs. Animals will be housed according to the best recommendations in a size appropriate environment with shelters and nesting materials. Tubes to act as hiding tunnels and shredding toys and wooden chewing toys for animals to gnaw on will also be supplied. When not having food intake actively measured, food will also be hidden in bedding and floor covering to give the animals the opportunity to forage. Health and welfare will be assessed daily by competent staffs to detect any upcoming problem at an early stage. By performing pilot studies and choosing well established protocols based on extensive previous experience, we will minimize the unknown effects on the mice and subsequently pain, distress and suffering. We will use non-invasive techniques wherever possible and use pain management when appropriate.We will use specific drugs and tools to target specific cell types and mechanisms, allowing a refined understanding of the pathways under investigation.

We will group-house mice whenever possible, and if single housing is required, we will monitor them to rapidly identify the potential development of behavioural symptoms or aggressive behaviours,

When possible, we will deliver substances via the oral route.