[redacted]

G: NON-TECHNICAL SUMMARY (NTS)

Please attach the Non-technical Summary as generated by your application in ASPeL.

Project Title
Glucocorticoids and stress in the development of diabetes and obesity

Duration of project - years
5
Duration of project - months
0

Purpose of the project (as in ASPA section 5C(3))
X (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 other abnormality, or their effects, in man, animals or plants;
(ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
(iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.
(c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b);
(d) protection of the natural environment in the interests of the health or welfare of man or animals;
(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;
(f) higher education or training for the acquisition, maintenance or improvement of vocational skills;
(g) forensic inquiries.

Keywords
Diabetes, Stress, Obesity, Steroid Treatment, Developmental Programming

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)
Stress is known to be a contributory factor in the development of obesity and diabetes, two of the biggest healthcare burdens in the UK at present, costing the NHS £10 billion per annum. To investigate the mechanisms involved in the development of these metabolic side effects, our objectives are four-fold.

1) To understand how glucocorticoids cause obesity and diabetes. Glucocorticoids are stress hormones, but synthetic forms can be used in the treatment of a wide range of disorders including asthma and rheumatoid arthritis. The incidence of diabetes is increased 48% in patients with rheumatoid arthritis treated with glucocorticoids for 6 months.

2) To develop treatment regimes to reduce or delay the occurrence of obesity and diabetes, using the knowledge gained from objective 1.

3) To examine how chronic stress leads to obesity and diabetes, by understanding both the early and late phases of this process.

4) To investigate the mechanism by which a mother's obesity can lead to obesity and diabetes in her progeny.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?
These studies will advance the knowledge of how stress and glucocorticoids can lead to development of diabetes and obesity. By understanding these mechanisms we are hoping be able to develop a dosing regime for glucocorticoids that may reduce some of these side effects. An alternative approach would be to develop a co-therapy (in conjunction with a pharmaceutical company) to reduce the obesity and diabetes associated with stress and glucocorticoids. The studies are also of direct relevance for veterinary medicine, as complications associated with chronically increased glucocorticoids levels are common in animals. Furthermore, we will be able to generate results which may influence maternity care to reduce obesity and diabetes in the next generation.

What types and approximate numbers of animals do you expect to use and over what period of time?
Over the 5 years of the project we expect to breed up to 7500 genetically modified mice Over the 5 years of the project we expect to use up to 5000 mice and 2100 rats

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels of severity? What will happen to the animals at the end?
Our experiments involve giving the animals cumulative mild stressors leading to an overall moderate experience up to a 4 week period (eg. damp bedding overnight, short periods of immobilisation in a tube (28mm diameter) with appropriate ventilation for up to 30 mins), altering their diet by feeding them an unhealthy high fat diet or restricting their food, or giving them glucocorticoids usually in their drinking water. These are mild stressors and are not expected to cause any lasting harm. Although, given the nature of the experiments, some of the mice may develop diabetes, leading to a moderate level of severity. Some animals will also undergo invasive surgery, where we implant drug delivery devices (in place of daily injections) or inject directly into the area of the brain we are interested in, to place drugs in this region or using technologies that will manipulate the pathways we are interested in. All our experiments will be designed to reduce the level of suffering or harm to the animals. At the end of the study or in the unlikely event that an animal is suffering, they will be killed humanely.

The 3Rs

Replacement

Non-animal alternatives, such as model cell systems, will be utilised for analysis of molecular pathways involved in glucocorticoid actions within brain cells and peripheral metabolic tissues (e.g. liver and adipose). However, the changes that occur in response to altered diet and/or glucocorticoids and stress affect whole-body energy metabolism and need ultimately to be studied in vivo. There is currently no cell system to replace assessment of whole animal's physiological responses.

Reduction

From our previous work we have experience of how to design the experiments to minimise the number of animals used in order to generate meaningful data. Statistical powering will be used to determine the minimum number of animals required to be able to detect the desired size of biological effect as statistically significant. This will be discussed with a biostatistician. In addition, where such data is available, the power analysis will be updated for a model periodically, as improvements over time may lead to a reduction in the number of animals required. Where needed, we are able to get advice from an experienced statistician to help plan any new experiments in order to get the maximum benefit.

Refinement

Our research projects will only use rodents. We are unable to use zebrafish or other lower organisms, as the models we require (such as diet-induced obesity) are established and validated in rats and mice. We will predominantly be using mice, as the mechanisms we are examining require knock-out models where genes have been manipulated within specific tissues.

We will specifically select acute and chronic stress models which cause the least pain or distress and that have been previously used and validated as being effective. Protocols where we modify diet are all known to have mild effects and any changes in glucose tolerance can be achieved with minimal distress. Part of our rationale is to evaluate stress hormones, and how these change in response to the manipulations used. Therefore we will monitor the stress hormones in many of our studies enabling quantification of the degree of stress in our models.