Progress report for Priya Sumithran

Endocrine Society of Australia Higher Research Degree Scholarship Recipient: 2007-2009

PROGRESS REPORT – 12 MONTHS

"Investigating physiological adaptations to weight loss contributing to weight regain"

1. Background

While humans can modulate food intake by voluntary control in the short term, the almost invariable weight regain that occurs in obese individuals after weight loss suggests that in the long term, biologically-determined feelings of hunger and satiety may be more important than voluntary control of food intake.

In the hypothalamus, neurotransmitters such as neuropeptide Y, agouti-related peptide, melanin concentrating hormone and others provide central regulation of hunger and satiety. It is likely that the levels of these neurotransmitters are controlled by peripheral signals including nutrients such as glucose, ketone bodies and free fatty acids, and hormones such as ghrelin, leptin, insulin, cholecystokinin, glucagon-like peptide, glucose-dependent insulinotropic peptide, pancreatic polypeptide, peptide YY and amylin, with others possibly yet to be described.

Leptin, a hormone synthesised in adipocytes (fat cells), signals to the brain to reduce food intake. Increasing evidence (including findings from a pilot study conducted in our laboratory) suggests that after diet-induced weight loss, changes in the levels of hormones and nutrients occur in a direction which encourages weight regain. One such change is a marked fall in the circulating level of leptin, which may result in hunger and lethargy. Other changes include a decrease in glucose, insulin, free fatty acids and triiodothyronine (T3), and an increase in reverse T3 and ghrelin. Little is known about the effect of diet-induced weight loss on the other hormones listed above.

It is unclear whether the nearly inevitable weight gain seen in individuals following weight loss is due to increased hunger resulting from the fall in circulating leptin and other hormonal changes, or whether it is due to the resumption of previous behavioural habits that sees the individuals return to their pre-weight loss eating patterns. The psychosocial factors which contribute to the success of the minority of people who do maintain a reduced body weight are also not well understood. This project aims to enhance our understanding of these issues, which would assist in the creation of more effective approaches to prevent weight regain after weight loss.

Furthermore, over recent years, the popularity of low carbohydrate diets as a means of rapid weight loss has resurged. It is anecdotally described that the ketosis associated with low carbohydrate diets reduces feelings of hunger, although the evidence regarding this has been conflicting. There is no clear consensus in the literature about what degree of carbohydrate restriction is required to produce ketosis. A smaller project has been undertaken to address this.

2. Hypothesis:
Our overall hypothesis is that weight regain after weight loss is not due primarily to voluntary return to previous lifestyle habits, but can be explained by changes in peripheral hormonal signals activating hunger and encouraging feeding behaviour.

Specific hypotheses:

1. That energy restriction, resulting in weight loss, will send a starvation signal(s) to the brain activating hunger and reducing satiety impulses.
2. That a prolonged period of maintenance of the lower body weight will not see the reversal of hormone and GI peptide profiles and ratings of hunger and satiety to levels seen prior to weight loss.
3. That elevated circulating ketone bodies suppress hunger.
4. That certain psychological, social or personality factors can predict individuals who are more likely to successfully maintain their weight loss.

Aims:
1. To examine in humans the (a) short and (b) long term effects of weight loss on basal and postprandial circulating peripheral nutrient and hormone levels and to relate these changes to ratings of hunger and satiety.

2. To test the hypothesis that ketosis leads to suppression of hunger and to examine the effect of ketones on the changes in basal and postprandial circulating nutrients and hormones.

3. To investigate if personality, social and behavioural factors can identify a person's likelihood of maintaining weight loss.

3. Progress to date
I have written a submission to the Austin Health Human Research Ethics Committee, and approval has been obtained for the main component of this project. Approval to use several questionnaires to assess psychosocial factors which predict successful weight maintenance has been requested and is pending. The selection of these questionnaires was made in consultation with colleagues in the department of clinical and health psychology.

Recruitment and screening of subjects has commenced, and first subjects will begin the weight loss phase of the study in mid-February 2008. It is anticipated that all subjects will have completed the study protocol by mid-late 2009.

A separate, related study, entitled "an investigation of the threshold for the development of ketosis with a low-carbohydrate diet" was conceived, planned, submitted to and approved by the Human Research Ethics Committee, undertaken and completed in 2007. This study involved restricting dietary carbohydrate intake to 3 different amounts in 12 subjects in random order, in an attempt to establish if there is a common threshold of carbohydrate intake below which ketosis occurs. 12 subjects were recruited and studied between July and December 2007. The results from this study are currently being analysed and prepared for publication.

A literature review of ketogenic diets undertaken during the planning of the above study resulted in the preparation of a review article, which has been accepted for publication.

4. Difficulties (past/current/future) and how addressed

The main problem to date is related to the subjects' difficulty in adherence to the VLED. This was identified in the ketosis study, and counselling was attempted with moderate success. There is certainly potential for this to be even more of a problem in the weight loss period of the main study, due to the greater intensity and duration of the VLED. More careful screening and counselling of subjects, written guidelines and regular follow-up have been instigated to prevent/minimise this.

5. Future experiments/analysis to complete research project

The bulk of the main project is still to be completed. This will include:

- completion of recruitment
- completion of 12 month protocol in all subjects
- testing of control subjects
- performing ketone infusion sub-study
- analysis of all blood samples and questionnaires
- analysis and interpretation of results

6. Publications

- Sumithran P, Proietto J. Ketogenic diets for weight loss: a review of their principles, safety and efficacy. *Obes Res Clin Pract* (in press – accepted 16/11/07)
- Sumithran P, Proietto J. Case report: safe year-long use of a very-low-calorie diet for the treatment of severe obesity. *Med J Aust* (in press – accepted 19/12/07)

It is expected that a manuscript regarding the study "An investigation of the threshold for the development of ketosis with a low-carbohydrate diet" will be submitted for publication in 2008.

7. Data presentations

- oral presentation at departmental seminars 16 May, 8 August, 10 October 2007
- planned oral presentation (Confirmation of Candidature) 8 April 2008