

# Laboratory rodents



## – an essential tool in the fight against human obesity

Laboratory rodents have proved to be useful models and sources of data for extrapolation to the human condition for many years. This is particularly true in the field of food intake and body weight regulation, which has obvious application to the growing obesity epidemic in the developed and developing world. Professor Julian Mercer describes some of the studies being undertaken at the Institute with the Siberian hamster, which demonstrates an amazing control over its body weight according to day length. This work is helping to increase our understanding of the complex networks of the body's 'signalling and response' systems, with which we must contend if we are to combat the consequences of our current 'obesogenic' environment.

As an example of the relevance of rodent models to man it is known that all gene mutations leading to obesity in mice find parallels in mutations in the same genes in humans, or have identified systems in which other human genes are mutated. So genes that are essential for normal body weight regulation in laboratory rodents are also essential for normal body weight regulation in humans. The leptin and melanocortin-4 receptor genes are good examples of this direct translation from rodent to human. The main expression sites in the context of obesity for these genes are white adipose tissue (fat) and the brain (hypothalamus), respectively. The obese ob/ob mouse results from a mutation in the leptin gene, and the equivalent genetically-inherited gene mutation in humans results in massive childhood-onset obesity, which can be successfully reversed by leptin therapy. Mutations in the melanocortin-4 receptor are the most commonly identified single gene cause of early onset obesity in humans.

Accordingly, much of the focus in the research area that encompasses obesity, body weight, food intake and energy balance has been on mutant and genetically-engineered rodent models, along with simple manipulations of energy balance such as food restriction. However, other less conventional animal models also have a lot to offer as we attempt to unravel the physiological regulation of feeding, energy balance and body weight.

### » Introducing the Siberian hamster – the master of weight control!

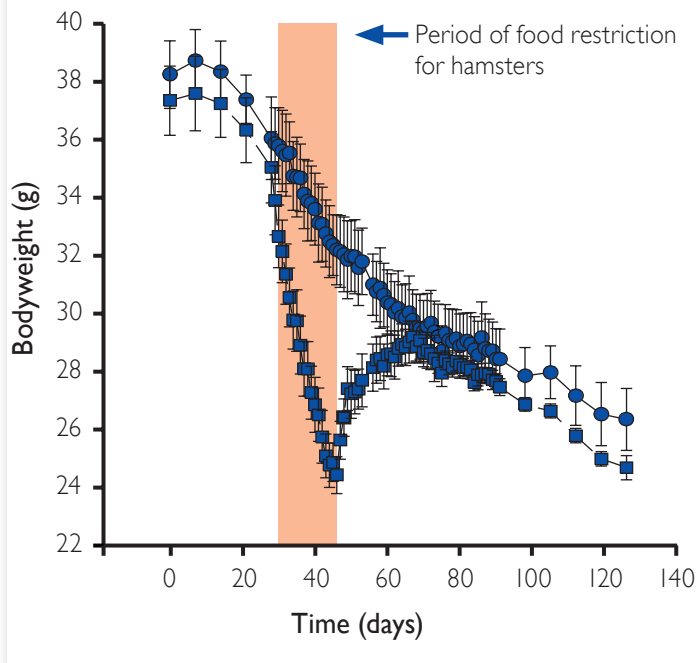
The Siberian hamster, *Phodopus sungorus*, responds in a dramatic way to a simple change in daylength or photoperiod. If these hamsters are transferred from a long summer-like photoperiod to a short winter-like photoperiod, they can reduce their body weight by up to 40% over a 12-16 week period, whereas the reverse manipulation can increase the body weight of individual animals by up to 50% in a 2 week period.

The potential power of this hamster model in the elucidation of mechanisms of body weight control is highlighted by studies where modest food restriction was imposed upon hamsters that were already losing weight as a consequence of being housed in a short photoperiod. As expected, the superimposed food restriction accelerated the rate of weight loss, causing body weight to fall below a seasonally-appropriate level. When food restriction was subsequently lifted, and the animals were again allowed to feed ad libitum, but were still held in short photoperiod, body weight increased, but not to its level at the beginning of the restriction period. Rather, once body weight reached a level similar to that of



hamsters with the same photoperiodic history that had been fed ad libitum throughout, weight gain was curtailed and body weight then began to decline again in parallel to the controls (figure 1). This manipulation provides some of the best evidence of direct regulation of mammalian body weight, and suggests the presence of a seasonal time-keeping mechanism that continues to adjust an encoded appropriate body weight even during weight loss due to imposed restriction.

### Evidence for sliding set point regulation of body weight in Siberian hamster



**Figure 1**

The maintenance of energy balance and an appropriate body weight involves a network of central and peripheral signalling systems. The hypothalamus at the base of the forebrain is a critical integratory centre in the regulation of food intake, energy balance and body composition. Some of our earlier work with this hamster model (Mercer *et al.*, 2001), backed up by a more recent study (Archer *et al.*, 2007), clearly indicates that the fascinating biological phenomenon depicted in Fig 1 is the result of two related but distinct processes. Firstly, the Siberian hamster is able to defend its body weight and composition from an imposed negative energy balance (e.g. food restriction) by compensatory changes in its hypothalamic systems that combine to reduce energy expenditure, thereby conserving energy while food supplies remain limited, and increase intake once food again becomes freely available. The functioning of these systems appears to be common to most mammals, and may underly the difficulty experienced by many people who attempt to lose weight by dieting. Secondly, the hamster is also able to programme changes in the level of body weight that it will attempt to maintain. So this species potentially provides access to novel mechanisms of body weight regulation beyond the powerful defence mechanisms 'designed' through evolution to prevent death from starvation.

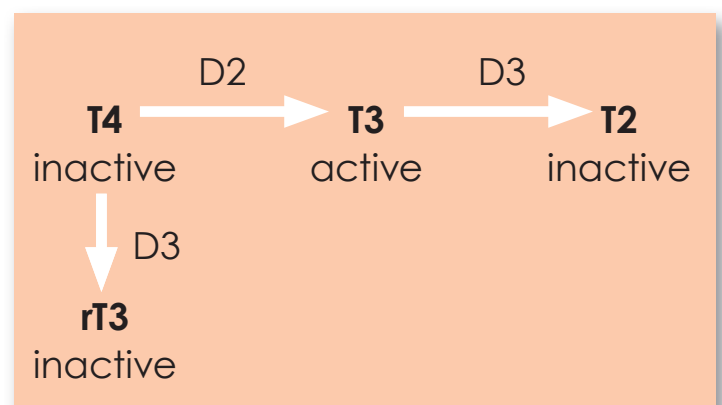
At the Rowett we maintain a colony of Siberian hamsters which we are using to investigate both the functioning of the known hypothalamic systems alluded to above, as well as attempting the identification and characterisation of novel components of the second regulatory system. Little is known of the signalling framework underlying the encoding of an 'appropriate' body weight, i.e. the determination of the level at which body weight will be maintained or 'defended'. It is clear, however, that the definition of such a system could have enormous implications, with the potential to allow weight to be lost without engaging the 'defence' mechanisms that frustrate conventional attempts at weight loss.

### ▶ The role of thyroid hormone in the brain's regulation of energy balance

Research into the components of a system that determines the level of body weight that will be defended is ongoing, but it has already drawn attention to a novel hypothalamic area that up until now has not been thought to be involved in the energy balance process. Recently, we have also uncovered a role for a group of cells called tanycytes, that line the third ventricle of the hypothalamus. Our work in the Siberian hamster shows that tanycytes are important in regulating the access of thyroid hormone to neurons of the hypothalamus (Barrett *et al.*, 2007). These neurons are amongst the most important for sensing hunger or satiety and regulating energy expenditure.

Thyroid hormone (T3) has been recognised for many decades as a hormone important in body weight regulation, but its role was largely thought to be the regulation of the metabolic rate of muscle and other organs within the body. There is little understanding of the role of T3 in the brain.

Thyroxine (or T4, so called because it contains 4 iodine molecules as part of the structure), is produced by the thyroid gland and is the precursor to T3, which is the form which is most active in the body. Activation of T4 occurs by the removal of an iodine molecule by an enzyme called type 2 deiodinase (D2). T3 can be metabolised to an inactive form (T2) by removal of another iodine molecule by an enzyme called type 3 deiodinase (D3). These deiodinase enzymes are expressed in tanycytes of the Siberian hamster and therefore the balance between inactive or active forms of T3 will depend on the presence or absence of one or both of type 2 or type 3 deiodinase (figure 2).



**Figure 2**