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Molecular genetics of body weight homeostasis

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Does body mass regulation breakdown via the development of leptin 'insensitivity'?

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The hypothalamus has been well characterised as the control centre for food intake and metabolism in laboratory rodents. In humans, single gene mutations and brain injury data confirm that this system is largely the same. In the hypothalamus a complex series of anorexigenic and orexigenic neuronal pathways interact with both peripheral short-term nutritional and satiety signals and longer-term body weight signals to ensure body mass homeostasis. However, the prevalence of overweight and obesity in the population is increasing. This, together with the fact that once obesity has developed, subsequent dietary intervention resulting in weight loss is extremely difficult to maintain, indicates both the weakness of this system in regulating over-feeding and also that the perception of body mass by the hypothalamus may be altered in obesity. Leptin, produced primarily by and in proportion to the amount of white adipose tissue, is an important hormone in body mass regulation stimulating anorexigenic and inhibiting orexigenic hypothalamic neurones, resulting in a reduction in food intake and an increase in energy expenditure. In obesity, circulating levels of leptin are high and evidence exists in both rodents and in humans of leptin 'insensitivity' negating or reducing the effects of the hormone. This insensitivity may occur at the hypothalamus or in the systems transporting leptin into the brain. In an attempt to understand the development of leptin 'insensitivity' we have used rodent models of varying adiposity, and hence varying levels of circulating leptin, to investigate changes in the central sensitivity to exogenously administered leptin. We have quantified leptin receptor gene expression, Ob-R and Ob-Rb, and measured ¹²⁵I-labelled leptin binding to assess the number of functional leptin receptors. The leptin inducible gene, encoding the suppressor of cytokine signalling 3 (SOCS3), was also quantified to assess the sensitivity of these receptors to leptin. Evidence for differential leptin sensitivity was found in the genetically obese *ob/ob* mouse, which lacks leptin and is hyper-sensitive to injected leptin due to the up-regulation of Ob-Rb. This indicates that central Ob-Rb gene expression is sensitive to the concentration of circulating leptin and hence the potential for down-regulation of the Ob-Rb gene in response to prolonged elevations in leptin concentration. In the Lou/C rat, which is smaller and has proportionately less white adipose tissue than the Wistar rat from which it is derived, we found elevated expression of Ob-R in the choroid plexus compared to the Wistar indicating a potential for increased transport of leptin into the brain. Also, in the photoperiodically sensitive Siberian hamster, which has a highly variable adiposity, the response to leptin challenge was variable depending on the ambient photoperiod indicating that sensitivity to leptin can be reversibly changed in this species. We are investigating the mechanisms underlying these changes in the transport of and sensitivity to leptin in the rodent models detailed above and in

cells transfected with leptin receptors tagged with green fluorescent protein. This will enable us to explore the possibility that the manipulation of leptin transport/sensitivity could provide potential therapeutic approaches to the treatment of obesity.

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Body weight homeostasis during pregnancy and lactation

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Oleylestrone and body weight homeostasis

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