**Sex-specific regulation of metabolism by leptin**

Thomas King1, Priyanka Singh1, Jennifer Oraha1, & Nicola J Lee1\*

1 Charles Perkins Centre, School of Medical Science, University of Sydney, Sydney, Australia

Fundamental sex-specific differences have been shown to exist in the regulation of metabolism however the underlying mechanisms remain largely unknown. We have recently shown that the resistance to the obesifying effect of a high-fat diet in female C57BL/6J mice is linked both to an ability to significantly reduce their respiratory quotient (RQ) as well as inherent sex differences in the catabolic versus anabolic neurological signalling pathways. One of the main peripheral hormones acting on these neurological signalling pathways to communicate energy status in the body is leptin, an adipocyte-derived hormone primarily secreted in direct proportion to fat mass. Dysregulated leptin signalling results in hyperphagia, obesity and type 2 diabetes. We have used a combination of leptin administration, comprehensive metabolic phenotyping, and sophisticated mapping of central leptin receptor (Lepr) expression to investigate sex-specific differences in the metabolic effects of leptin in mice. Interestingly, the ability of leptin to reduce food intake was only evident in male but not female mice. In contrast, females showed a marked reduction in RQ in response to leptin, independent of food intake or energy expenditure. Critically, this reduction in RQ led to a significant reduction in body weight. Whilst Lepr expression in the hypothalamus was comparable between sexes under normal conditions, female mice displayed a 2-fold increase in Lepr expression in the dorsal nucleus raphe, a region of the brainstem involved in appetite regulation. Furthermore, after 4 weeks of high-fat diet feeding, male mice show a marked reduction in central Lepr expression which is not evident in female mice. These findings suggest that leptin has different metabolic effects in female compared to male mice, at least partially due to differing central Lepr expression patterns. The resistance to the obesifying effect of a high-fat diet in female C57BL/6J mice may be due to an ability to retain central Lepr expression. Taken together, these results have important implications for the management of obesity and type 2 diabetes in humans and draw attention to the need to include both sexes in metabolic studies.