



## Energy homeostasis and running wheel activity during pregnancy in the mouse



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### ARTICLE INFO

#### Keywords:

Pregnancy  
Running wheel  
Activity  
Food intake  
Energy expenditure

### ABSTRACT

Pregnancy and lactation are metabolically challenging states, where the mother must supply all the energy requirements for the developing fetus and growing pups respectively. The aim of the current study was to characterize many aspects of energy homeostasis before and during pregnancy in the mouse, and to examine the role of voluntary activity on changes in energy expenditure during pregnancy. In a secondary aim, we evaluate measures of energy homeostasis during pregnancy in mice that successfully reared their litter or in mice that went on to abandon their litter, to determine if an impairment in pregnancy-induced adaptation of energy homeostasis might underlie the abandonment of pups soon after birth. During pregnancy, food intake was increased, characterized by increased meal size and duration but not number of meals per day. The duration of time spent inactive, predicted to indicate sleep behaviour, was increased both early and late in pregnancy compared to pre-pregnancy levels. Increased  $x + y$  beam breaks, as a measure of activity increased during pregnancy and this reflected an increase in ambulatory behaviour in mid pregnancy and an increase in non-ambulatory movement in late pregnancy. Energy expenditure, as measured by indirect calorimetry, increased across pregnancy, likely due to the growth and development of fetal tissue. There was also a dramatic reduction in voluntary wheel running as soon as the mice became pregnant. Compared with successful pregnancies and lactations, pregnancies where pups were abandoned soon after birth were associated with reduced body weight gain and an increase in running wheel activity at the end of pregnancy, but no difference in food intake or energy expenditure. Overall, during pregnancy there are multiple adaptations to change energy homeostasis, resulting in partitioning of provisions of energy to the developing fetus and storing energy for future metabolic demands.

### 1. Introduction

Pregnancy is a metabolically demanding state as, in addition to meeting her own increased energy requirements, the mother must supply the growing fetus with all of its energy needs. Following pregnancy, lactation presents the mother with further metabolic demands, and while food intake can increase upwards of 300% of virgin levels in lactating rodents, lactating mice and rats are typically in a state of negative energy balance as their food intake is still insufficient to completely meet with the energy requirements for milk production [1]. In anticipation of these energy demands, pregnant females show several metabolic adaptations that result in deposition of fat during pregnancy [2–4]. Thus, pregnancy is not simply about supplying energy to the growing fetus, but also storing energy for the future metabolic demands of lactation. This state of positive energy balance is characterized by increased food intake, fat deposition, and leptin and insulin insensitivity [5,6] although many other aspects of energy homeostasis, such as activity and energy expenditure during pregnancy [7,8], are less

well-characterized. In humans, energy expenditure is increased during pregnancy, due to an elevated resting metabolic rate and increased synthesis of new tissue, and it is thought that a decrease in activity may help compensate for the increased energy demands of pregnancy [9]. The mechanisms driving these changes in energy expenditure or activity remain unknown. The aim of the current study was to investigate many aspects of energy homeostasis in the mouse and examine the role of voluntary activity on changes in energy expenditure during pregnancy. *Ad libitum* access to a running wheel was used to monitor voluntary physical activity. Access to a running wheel during pregnancy has shown to have long term benefits on the health, particularly glucose regulation, of offspring [10,11]. Thus, understanding maternal energy homeostasis when there is access to a running wheel is important for the future investigation into how maternal exercise influences long term health outcomes of the off-spring.

Optimal adaptation of energy homeostasis to pregnancy is required for the long-term health of offspring. Numerous studies have investigated the effects of either maternal over-nutrition, such as obesity

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or high fat diet, or under-nutrition on the long-term health of the offspring and have shown these can negatively impact many aspects of health for the offspring, including body weight regulation, glucose homeostasis, brain development and immune function [12–15]. In the short term, optimal adaptation of energy homeostasis would also likely be an important factor for the success of reproductive efforts. In laboratory mice, it is not an infrequent event that a female mouse will give birth and then apparently abandon or kill the litter of pups [16,17]. Little is known about why mother-litter dynamics are not successful in these situations [16,18]. Hence, as a secondary outcome of the current study, we were able to retrospectively evaluate measures of energy homeostasis during pregnancy in mice that successfully reared their litter or mice that went on to abandon their litter, and thus to investigate the hypothesis that pup abandonment may be related to impaired adaptation in energy homeostasis during pregnancy.

## 2. Methods

### 2.1. Mice

A number of studies were carried out to investigate changes in energy homeostasis during pregnancy in the mouse. To characterize energy homeostasis during pregnancy in the mouse, virgin C57BL/6J female mice were used and longitudinal data comes from mice which had access to running wheels. Running wheel activity during lactation was measured in a different cohort of C57BL/6J female mice. To investigate energy homeostasis in late pregnancy and in the non-pregnant state, without the presence of a running wheel, a third cohort of virgin C57BL/6J female mice was used. To characterize running wheel activity across the estrous cycle, a fourth cohort of virgin C57BL/6J female mice was used. To examine the effect of change rooms and being housed without the running wheels for a short period (which happened when mice were mated in the first study mentioned above), a fifth cohort of virgin C57BL/6J female mice were used. In a final study, that of retrospective analysis of energy homeostasis during pregnancy in mice that had lost their litter in the early postpartum period or successfully weaned their pups, experimental data was pooled from a number of studies (using the data from only the control mice in these studies) carried out in our laboratory. This studied involved both the C57BL/6J female mice used in the experiment characterizing energy homeostasis during pregnancy and also a number of studies in which  $Prlr^{fllox}$  mice on C57BL/6J background were used as the control group (see [19] for details of the generation of these mice). There have been no previously found differences between these  $Prlr^{fllox}$  mice and our C57BL/6J mice.

For long-term data collection prior to pregnancy and then during pregnancy, virgin C57BL/6J female mice (starting age of 8–10 weeks) were housed in metabolic and behavioural phenotyping cages (Promethion, Sable Systems International). Data were collected on body weight changes, food intake and feeding behaviour, running wheel activity, infrared beam breaks as a measure of activity, and oxygen consumption and carbon dioxide production to determine energy expenditure by indirect calorimetry. Mice were initially housed in the metabolic and behavioural phenotyping cages for 2 weeks (pre-pregnancy), then moved to another room to be housed with a stud male in normal home cages, and then returned to metabolic cages when a vaginal plug was detected. Day of plug was assigned as day 1 of pregnancy. Typically, our mice give birth on day 20 of pregnancy, however day 19 was also common, and while we have continuous data throughout parturition and early lactation, for most comparisons we present the data from day 1 of pregnancy up until and including day 18. Mice were then left undisturbed until 4–5 days after giving birth, at which time the number of pups was counted. Visual assessment of the mice took place daily throughout the study and day of first appearance of pups was recorded. If mice had demonstrated a plug indicating successful mating and yet there was no evidence of increased weight

gain and/or delivery of pups then these mice were excluded from the data collection and assumed to be ‘pseudopregnant’. Metabolic and behavioural data were collected in the non-pregnant state and then for the duration of pregnancy and the early postpartum period till approximately day 4 or 5 after birth. A second cohort of mice ( $n = 6$ ) were similarly treated yet they remained in the metabolic cages for the duration of lactation (three weeks) and for the week following weaning/removal of their pups.

While data was collected throughout the reproductive cycle period, file size restricted the length of time data could be collected continuously, and on days when data recording was stopped and restarted these days are excluded from the 24 h data analysis and hence the ‘n’ value for each data point varies slightly. Typical recording duration was 6 or 7 days. Mice were individually housed in a temperature- and lighting-controlled environment ( $23 \pm 1$  C, 12 h light: 12 h darkness, lights on at 0700) and allowed access to standard rodent chow and water *ad libitum*. All experimental protocols were approved by the University of Otago Animal Ethics Committee.

In a second experiment, with a different cohort of mice, late pregnant (day 14–18 of pregnancy) C57BL/6J mice and aged matched virgin controls were housed in the metabolic and behavioural phenotyping cages (Promethion, Sable Systems International) for 3 to 4 days without running wheels being present in the cages.

### 2.2. Body weight

Total body weight gain during pregnancy was determined by the highest body weight measured for each mouse at the end of pregnancy, minus initial body weight on day 1 of pregnancy. Post-birth body weight was estimated by selecting the lowest body weight recorded in the 24 h following birth. Approximate change in body weight of the mother independent of conceptus was estimated by comparing post-birth body weight and day 1 of pregnancy body weight. Cumulative body weight gain graphs were generated using the average body weight from each day of pregnancy for each mouse. Body weight gain in the first week of pregnancy was compared to change in body weight across the 7 days prior to being housed with the stud male.

### 2.3. Food intake

Total food intake for each day (24 h period) during pregnancy, and in the non-pregnant state (averaged over 5 days) was measured. The percentage of food consumed in the dark phase of the light cycle was determined by calculating dark phase food consumption/total food consumption. The number of feeding bouts (‘meals’) per day was calculated, with a meal defined as a reduction in weight of the food hopper with a minimum intake duration of 30 s. Time spent eating was defined as the time the mouse interacted with the food hopper and there was a reduction in weight of the food hopper, with a maximum “within-intake” pause of 150 s allowed. Meal duration was considered as the total time of each meal, as defined above, and meal size was defined as the total amount of food consumed during each meal.

### 2.4. Energy expenditure and running wheel activity

Energy expenditure was determined by indirect calorimetry using both  $VO_2$  (oxygen consumption) and  $VCO_2$  (carbon dioxide production) measurements. Respiratory exchange ratio (RER) was also determined throughout pregnancy. Voluntary activity, measured in distance, on the running wheel was examined across pregnancy. Time spent running was considered the duration the mouse spent interacting with the running wheel when there was an increase in wheel rotations. In the second study, parameters were measured in another cohort of mice in the absence of the running wheel in the cage.

To examine the influence of estrous cyclicity on running wheel behaviour, a separate group of virgin C57BL/6J female mice were

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