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Metabolic consequences of timed feeding in mice

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HIGHLIGHTS

- We studied the effects of feeding during the light or dark period in mice kept on long or short days.
- Body weight was unaffected by either long or short photoperiod or feeding time.
- Restricted feeding had the largest metabolic impact on mice exposed to long days versus short days.
- Glucose tolerance was impaired at the end of the light period in light fed compared to dark fed mice.
- Changes in liver gene rhythms did not correlate with changes in feeding time.

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ABSTRACT

The time of day at which meals are consumed is known to impact on behaviour as well as physiological systems. In this study we investigated the behavioural and physiological effects of restricting access to food to the light or dark period in mice maintained on either long or short photoperiods. In both photoperiods, wheel running commenced upon the onset of darkness and was generally confined to the period of darkness. Provision of food during light provoked an anticipatory burst of activity several hours before feeding in both photoperiods. After 28 days on the feeding schedule, body weight was unaffected by either photoperiod or feeding time. Plasma insulin was increased and glucose and triglycerides tended to be lower in mice fed during the light period and sampled 2 h after lights off compared to the dark fed mice. Mice fed during the light while on long day length had improved glucose tolerance and whole body insulin tolerance when tested 2 h after lights on. This was not evident in mice kept on the short photoperiod. Because these observations were confounded by the time since their last meal, we undertook a study of glucose tolerance across 24 h in mice on the long photoperiod after a 2 hour food withdrawal. A clear rhythm of glucose tolerance was observed in mice fed during the light period with maximal glucose tolerance just prior to the expected presentation of food and minimal tolerance 2 h before lights off. By contrast, no rhythm in glucose tolerance was observed in the dark fed mice, but maximal glucose tolerance occurred 2 h before lights off. To investigate the evolution of the physiological adaptations, mice on this feeding/photoperiod regime were studied after 7 or 35 days. After 7 days the corticosterone rhythm was not different between light and dark fed mice, but by 35 days peak corticosterone secretion occurred a few hours before food presentation in both groups representing an 8 hour shift. The rhythm of expression of liver *Bmal1* mRNA was similar in light and dark fed mice after 7 and 35 days on the schedule while the *Per1*, *Per2*, *Nr1d1* and *Dbp* mRNA rhythms were delayed on average by 3.5 ± 1.1 h and 3.7 ± 0.9 h in light fed mice after 7 and 35 days respectively compared to dark fed mice. Rhythms of metabolically important genes were shifted in light fed mice compared to dark fed, by 5 h or became arrhythmic. This study shows that not only circadian rhythms facilitate metabolic control, but also different environmental events, including season and feeding opportunities, alter aspects of circadian and metabolic physiology.

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1. Introduction

There is emerging evidence that the time of day at which food is consumed influences weight gain and metabolic function. In recent human weight loss studies, participants who voluntarily confined or were randomised to confine the majority of their energy intake to early in the day lost more weight [1,2] and had a greater improvement in insulin sensitivity, triglycerides and oral glucose tolerance [2] than those ingesting a similar diet later in the day. Similarly there is evidence to suggest that shiftworkers who have altered patterns of light exposure, sleep and meal times are at an increased risk of developing obesity and metabolic syndrome [3,4]. Furthermore, the duration of sleep alters

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metabolism such that people who sleep less than 5 h or longer than 8 h a night are at increased risk of developing obesity and metabolic disorders [5].

The circadian timing system is implicated in the phenomena mentioned above. Rhythmicity within the suprachiasmatic nucleus of the hypothalamus is generated by a suite of genes, known as clock genes, which include *Bmal1*, *Clock*, *Per1*, *Per2*, *Cry1*, *Cry2* and *Nr1d1* (also called *Rev erb a*) [6]. Positive and negative feedback loops involving interactions of their protein products on their own gene promoters establish a near 24 hour cycle within the cells. Two of the proteins, BMAL1 and CLOCK also provide an output signal via interactions with promoters on other transcription factors and functional genes. The SCN rhythmicity is entrained to the environment by neural input from the retina and influences a wide range of physiological systems, utilising multisynaptic neural pathways (e.g., to the pineal gland, adrenal gland and liver) and hormonal routes (e.g., cerebrospinal fluid arginine vasopressin and prokineticin 2). It is well established however, that peripheral tissues like the liver and muscle also have the capacity to generate cellular rhythmicity via the same genes and that while generally the rhythms are entrained by the SCN, under certain circumstances they can operate in the absence of SCN cues.

Cellular rhythmicity, while being driven by SCN cues and endogenous timing mechanisms, is also responsive to metabolic state. For example, the transcription factors PPARα [7,8] and PGC1α [9] bind to the promoters of core clock genes *Bmal1* and *Nr1d1*, driving their transcription. At the protein level, the metabolic sensor, AMP activated protein kinase (AMPK) phosphorylates proteins involved in the negative arm of the cellular clock, targeting them for degradation and hence altering the phase of rhythmicity [10]. Other metabolically important protein kinases (GSK3β, MAPK) similarly target some core clock proteins for phosphorylation and subsequent degradation [11–15], whereas phosphorylation of PER2 and NR1D1 proteins by GSK3β is important for their stabilisation and nuclear translocation [16,17]. Alternatively, the nicotinamide adenine dinucleotide (NAD+) dependent histone deacetylase sirtuin 1 (SIRT1) which associates with and modulates the activity of CLOCK:BMAL1 driven gene expression [18] is also known to target PER2 protein for degradation [19]. These mechanisms, amongst others, intricately link nutrient state and circadian rhythms, thereby optimising the timing of metabolic processes.

Disruption of rhythmicity through alterations to the various clock genes has a range of physiological consequences. Mice carrying a mutation in the core clock gene, *Clock* lack cellular rhythmicity in peripheral tissues such as the liver (but not central rhythmicity [20]) and have abnormal, strain dependent metabolic phenotypes, including obesity, hyperleptinemia, hyperlipidemia, hepatic steatosis, hyperglycemia, hypoinsulinemia [21], elevated levels of the adipokines, leptin and adiponectin [22,23], impaired glucose stimulated insulin secretion, impaired glucose tolerance and paradoxical improved insulin sensitivity [22,24]. Similarly, mice that lack central and peripheral rhythmicity (e.g., *Bmal1* null mice) exhibit a more severe metabolic phenotype, in particular, altered fat deposition and adipokine secretion [25,26].

Laboratory rats and mice are nocturnally active and when food is available ad libitum they will consume 60–70% of their food during darkness when held on the traditional 12L:12D photoperiod [27,28]. When food is made available to rats and mice only during the resting light phase, the clock gene expression rhythm in the liver and other peripheral tissues is shifted by approximately 12 h within 5 to 7 days [29,30], but not the SCN [29] or its direct targets (e.g. pineal gland [31]). Manipulation of the time of feeding has been observed to alter body weight, metabolism and clock gene expression [32–34]. There have been no studies, however, on the influence of restricted feeding during long (summer) or short (winter) photoperiods on metabolic function of mice.

In the current study we addressed several questions. (1) What is the impact of providing food access exclusively during the light or dark period on the body composition, plasma triglycerides, glucose and insulin in mice kept on long or short photoperiods? (2) What is the effect of light and dark feeding on glucose, insulin, corticosterone and triglyceride rhythms in mice maintained on a long photoperiod for 7 or 35 days? (3) What is the effect of light and dark feeding on glucose tolerance across 24 h in mice maintained on a long photoperiod for 28 days? (4) What is the effect of light and dark feeding on liver gene rhythmicity in mice maintained on a long photoperiod? (5) If there are changes in glucose tolerance, what are the changes in the expression of an a priori selected set of key metabolic genes across 24 h? We predicted that since the difference in time of presentation of food under the 2 schedules was 8 h, physiological rhythms would also be altered by 8 h.

2. Material and methods

2.1. Animals

Male C57BL/6 mice aged 4 weeks old were purchased from the Animal Resources Centre (Canning Vale, Western Australia) where they had been kept on a 12L:12D photoperiod and maintained on ad libitum standard chow and water. All the experimental protocols were approved by the University of Adelaide Animal Ethics Committee.

2.2. Experiment 1

To understand the impact of short and long photoperiods and restricted food availability on behaviour, two groups of 10 mice were entrained for four weeks to either 16 h of light and 8 h of darkness (16L:8D) or 8 h of light and 16 h of darkness (8L:16D) with food and water available ad libitum. Thereafter food was made available continuously ($n = 2$) or exclusively during the light ($n = 4$) or dark ($n = 4$) periods for each group. The time of day is designated as Zeitgeber time where ZT0 = time of lights off for both photoperiods. Food pellets were manually removed from or replaced into the cage-lid hoppers. Wheel running rhythmicity was monitored in individual mice housed in light-controlled chambers in cages equipped with 11.5 cm diameter running wheels and magnetic micro-switches. A data acquisition system (LabPro, Data Sciences, St. Paul, MN) was used to record the number of wheel rotations in 10 minute bins. The data was processed in Excel and visualised using the Actiview software package (MiniMitter, Bend, OR).

2.3. Experiment 2

Mice were group housed ($n = 6$ per cage) in light-controlled chambers and entrained to either 16L:8D or 8L:16D for 4 weeks with food and water available ad libitum. Thereafter at the transition to and from darkness, empty or filled lid food hoppers were exchanged to make food available exclusively during the light or dark period. The food intake was estimated by weighing the food left over in the hoppers or retrieved from the floor of the cages each week when the mice were moved to clean cages.

After four weeks of timed feeding, intraperitoneal glucose tolerance tests (IPGTT) were performed 2 h after lights on following an overnight fast. Mice were injected with glucose (1 g/kg, Sigma, St. Louis, MO) and blood collected from the tail vein (5 μl) just prior to the injection and 15, 30, 60, 90 and 120 min post glucose injection. The blood glucose level was measured using a HemoCue Glucose 201+ Analyser (HemoCue, Angelholm, Sweden). Following the IPGTT the restricted feeding schedule continued.

One week later, Intra Peritoneal Insulin Tolerance Tests (IPITT) were performed. Food was withdrawn from the cages at lights on for both photoperiods and 2 h later the mice were injected with insulin (0.75 m IU/kg, Actrapid) and blood collected just prior to the injection and 15, 30, 60, 90 and 120 min post insulin injection for glucose measurement. Following the IPITT the restricted feeding schedule continued.

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