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Differential effects of the circadian system and circadian misalignment on insulin sensitivity and insulin secretion in humans

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Abstract

Glucose tolerance is lower at night and higher in the morning. Shift workers, who often eat at night and experience circadian misalignment (i.e., misalignment between the central circadian pacemaker and the environmental/behavioral cycles), have an increased risk of type 2 diabetes. To determine the separate and relative impacts of the circadian system, behavioral/environmental cycles, and their interaction (i.e., circadian misalignment) on insulin sensitivity and β-cell function, we used the oral minimal model to quantitatively assess the major determinants of glucose control in 14 healthy adults, using a randomized, cross-over design with two 8-day laboratory protocols. Both protocols involved 3 baseline inpatient days with habitual sleep/wake cycle, followed by 4 inpatient days with same nocturnal bedtime (circadian alignment) or with 12-h inverted behavioral/environmental cycles (circadian misalignment). Our data showed that circadian phase and circadian misalignment affect glucose tolerance through different mechanisms. While the circadian system reduces glucose tolerance in the biological evening compared to the biological morning mainly by decreasing both dynamic and static β-cell responsivity, circadian misalignment reduced glucose tolerance mainly by lowering insulin sensitivity, not by affecting β-cell function.

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Author contributions

J.Q., C.J.M., and F.A.J.L.S. conceived the idea and designed the study. C.J.M. and F.A.J.L.S., performed research; J.Q., C.D.M., and C.C. analyzed data; J.Q. and F.A.J.L.S. wrote the manuscript; J.Q., C.D.M., C.J.M., C.C., and F.A.J.L.S. interpreted the data and edited the manuscript.

1. Introduction

Glucose tolerance varies greatly across the day in healthy humans, peaking in the morning and with low levels in the evening/night. Diminished insulin sensitivity and β-cell function, two major determinants of type-2 diabetes (T2D) risk, are responsible for decreased glucose tolerance in the evening[1, 2]. Both the endogenous circadian system and behavioral/environmental cycles (e.g., fasting/feeding, sleep/wake, physical activity, and dark/light cycles) contribute to the diurnal variations in glucose control[3]. However, since these two factors typically cycle in synchrony in diurnally-active individuals, it is impossible to assess their separate contribution under normally entrained conditions (i.e., sleep at night, eating during the day). Furthermore, night shift workers chronically experience recurrent circadian misalignment, a condition where environmental/behavioral cycles are out-of-sync with the endogenous circadian system. This circadian misalignment may explain, in part, why shift work increases T2D risk[4]. Thus, understanding the separate and relative contribution of the endogenous circadian system and circadian misalignment—after accounting for behavioral cycle effects, on different components of glucose control is important for the general population and for shift workers.

We are not aware of any studies that could systematically address the independent effects of behavioral cycles, the endogenous circadian system, and circadian misalignment on insulin sensitivity and β-cell function in humans. This is partly because the gold-standard methods to quantify insulin sensitivity and insulin secretion (e.g., intravenous glucose tolerance tests, hyperglycemic clamp, euglycemic-hyperinsulinemic clamp) require long fasting durations and artificial manipulations of glucose levels. Thus, implementing such tests in a circadian protocol disrupts the fasting-feeding cycle and physiology, thus making it very difficult to design a balanced study to mathematically separate behavioral, circadian phase and circadian misalignment effects. The oral minimal model method that quantifies insulin sensitivity and β-cell responsivity from a mixed-meal test[5], allows us to circumvent above limitations and perform in-depth assessments of glucose control in two separate 8-day in-laboratory protocols with randomized, cross-over design.

2. Method

Other aspects of this study—which was designed to test separate hypotheses—have previously been published[6, 21, 22, 23, 24].

2.1 Participants and Experimental Design

Fourteen healthy nonsmoking, drug- and medication-free (excepting oral contraceptives) adults completed this study [mean age±SD, 28±9 y; BMI, 25.4±2.6 kg/m^2; HbA1C, 5.38±0.26%; eight men]. Identical mixed meals (33.3% of calculated daily calorie intake) given 1-h and 13-h following scheduled wake time. Fasting blood was drawn 7 min before the mixed meal, and postprandial blood was drawn every 10 min for 90 min, starting 10 min after the participant began eating the test meal, and subsequently every 30 min for the next 90 min, totaling 3 h. Details of methods, subject recruitment, screening, pre-inpatient study conditions, diet, and mixed-meal test can be found elsewhere[6].

2.2 Data Analysis and Statistics

Oral minimal model method—*Insulin sensitivity (S_I)* was estimated from plasma glucose and insulin concentrations measured during 3-hr mixed-meal tests using the oral glucose minimal model[7], which measures the overall effect of insulin on stimulating glucose disposal and inhibiting glucose production and has been successfully validated against model-independent measurements using multiple-tracer meal protocols and euglycemic-hyperinsulemic clamps.

β-cell function was quantified from C-peptide and glucose data using the C-peptide minimal model[5]. Basal β-cell function (Φ_b) and static β-cell function (Φ_s) measure insulin secretion in response to the basal glucose concentration or a given increment in glucose above basal glucose concentrations, respectively. Dynamic β-cell function responsivity (Φ_d) measures the stimulatory effect exerted by the rate of increase in glucose concentration on insulin secretion. Φ_d is likely to represent secretion of promptly releasable insulin, Φ_s reflects the provision of new insulin into a releasable pool. Total β-cell responsivity to glucose (Φ_{tot}), a measure of overall insulin secretion, can be calculated from Φ_s and Φ_d[8]. Finally, the disposition index (DI), assessing the appropriateness of insulin secretion for the prevailing level of insulin resistance, was calculated by multiplying Φ_{tot} by S_I.

Statistics—Analyses for mixed-meal tests were performed on natural log-transformed data. Results for transformed parameters were back-transformed (exponentiated) and reported on the original scale. Estimates for log-normally distributed data were reported as geometric means (95% CI). Linear mixed models with participant as random factor, tested the independent effects of the behavioral cycle [breakfast vs. dinner (1h or 13h after wake time, respectively)], circadian phase [8AM (biological morning) vs. 8PM (biological evening)], alignment condition (circadian alignment vs. circadian misalignment), and their interaction with test day (first vs. third) on S_I, Φ indices, and DI. Statistical significance was accepted as $P<0.05$.

3. Results

We did not find any significant interaction effects between duration of exposure (i.e., test day) and the main effects (i.e., circadian phase, circadian misalignment, and behavioral cycle; all $P\geq0.088$). Therefore, all the percentage changes and geometric means were calculated with test day 1 and 3 combined.

Circadian phase effects, independent of behavioral cycle effects: β-cell function was higher in the biological morning than in the biological evening (Fig.1 and 2, left panels)

All measures of β-cell function were lower in the biological evening than biological morning, with Φ_b by 13.7% (95% CI 6.6, 20.4 ; $P<0.0001$), Φ_d by 21.6% (95% CI 4.7, 35.6; $P=0.0086$), Φ_s by 11.3% (95% CI 1.2, 20.3,; $P = 0.034$), and Φ_{tot} by 14.7% (95% CI 2.0, 21.0; $P=0.022$). Similar results were found for DI, with a 19.1% reduction in the biological evening (95% CI 4.7, 31.4; $P = .0.0034$). There was no significant circadian effect on S_I (95% CI −4.2, 19.0; $P=0.06$).

Circadian misalignment reduced insulin sensitivity independent of circadian phase or behavioral cycle effects (Fig.1 and 2, middle panels)

S_I was 16.5% lower in the circadian misalignment than alignment condition (95% CI 7.9, 24.3; P=0.0007). There were no significant effects of circadian misalignment on β-cell responsivity, as all Φ indices and DI did not significantly differ between circadian alignment and misalignment conditions (all P>0.099).

Behavioral cycle effects, independent of circadian phase effects: Insulin sensitivity was lower at dinner than at breakfast, while β-cell function in response to meal was higher at dinner than at breakfast (Fig.1 and 2, right panels)

S_I was 25.4% lower (95% CI 13.2, 35.9; P<0.0001) at dinner than at breakfast. While no significant difference in Φ_b (95% CI −2.0, 12.3; P=0.054), Φ_{tot} was 14.7% higher at dinner than at breakfast (95% CI 2.3, 28.5; P=0.0046) due to increased Φ_s by 15.0% (95% CI 3.0, 28.4; P=0.0046) without significant difference in Φ_d (95% CI −3.1, 39.0; P=0.0579). DI was 14.4% lower at dinner than at breakfast (95% CI −3.3, 29.2; P=0.038).

4. Discussion

Our results revealed that the endogenous circadian system and circadian misalignment, after controlling for behavioral cycle influences, have independent and differential impacts on insulin sensitivity and β-cell function in healthy adults. First, the endogenous circadian system strongly regulated all aspects of β-cell function, without significant effect on insulin sensitivity. Φ_b, representing fasting β-cell responsivity, was lower in the biological evening. Furthermore, because Φ_d assesses insulin secretion in response to the maximum glucose increase after meal ingestion, the lower Φ_d in the biological evening reveals that the circadian system governs multiple immediate steps in the insulin secretory pathway (e.g., glucose sensing, rate of granule docking, priming, and exocytosis)[5]. Circadian regulation also likely influenced the distal steps in the insulin secretory pathway (e.g., incretin stimulation, synthesis, processing, granule maturation) because Φ_s was also lower in the biological evening[5]. The 14.7% decrease of Φ_{tot} in the biological evening is of particular clinical relevance, since the magnitude of change is similar to the difference between elderly and young individuals[9]. Our results are consistent with the study by Sharma *et al.* in which rotating shift workers had impaired β-cell function in the evening of their night shift as compared to in the morning of their day shift[10]. However, our design further allows us to distinguish whether such decline of β-cell function during night shifts is due to circadian phase and/or circadian misalignment, indicating a clear effect of the circadian phase, but not misalignment, on β-cell function. The circadian regulation of β-cell function may provide an explanation for the increased risk of poor glycemic control in late eaters and shift workers who often eat in the biological evening/night[11, 12]. Our results also support the findings that avoiding large meals with high glycemic index in the late evening or nighttime may prevent postprandial hyperglycemia, thus reduce the risk of T2D in the long run[13].

Furthermore, our finding that circadian misalignment specifically reduced insulin sensitivity, without significantly changing any β-cell responsivity indices or DI, is consistent with Leproult and colleagues' findings[14], showing that prior circadian misalignment in men,

independent of sleep loss, decreased insulin sensitivity without significant reduction in DI. Our results also agree with the study by Bescos et al reporting reduced insulin sensitivity after four days of simulated night shift using hyperinsulinaemic-euglycaemic clamp [25]. However, our participants consumed highly-controlled diet throughout the two protocols, which minimized the potential influences caused by variations in caloric intake. The 16.5% decrease in S_I upon exposure to circadian misalignment is notable, since this is about one-third of the difference in S_I between elderly and young individuals[9]. The decrease in S_I during circadian misalignment may be, in part, due to the increased growth hormone and fasting free fatty acid levels during nighttime wakefulness that we reported[6] because both decrease insulin sensitivity[15, 16]. In our short-term circadian misalignment exposure (3 days), we found no evidence of altered β-cell function due to circadian misalignment. However, the insulin resistance induced by circadian misalignment increases insulin demand, which—upon chronic exposure—may impair β-cell function, thus resulting in T2D. Indeed, other studies using longer term circadian disruption including clock gene knock-out and constant light exposure in rodents and prolonged misalignment together with sleep deprivation in humans did show β-cell dysfunction[17-19].

As for the independent effects of the behavioral cycle, S_I was lower at dinner than at breakfast, while β-cell function was higher at dinner. Previous studies have reported that under normally-entrained conditions (i.e., sleep at night, evening dinner), insulin sensitivity and β-cell responsivity peak in the morning, and deteriorate as the day progresses[1, 2]. Here, we show that such decrease in insulin sensitivity is mostly caused by the behavioral cycle, while the circadian system dominates the deterioration in β-cell responsivity. Interestingly, the behavioral cycle itself significantly improved total β-cell responsivity, specifically static response (Φ_s), at dinner. This may be partially explained by a phenomenon called “second meal effect”[20], in which the magnitude of insulin release is enhanced by previous glucose exposure.

In conclusion, the results show separate effects of the endogenous circadian system, the behavioral cycle, and circadian misalignment on insulin sensitivity and β-cell responsivity with relevance for daily glucose regulation in diurnally active people as well as night shift workers.

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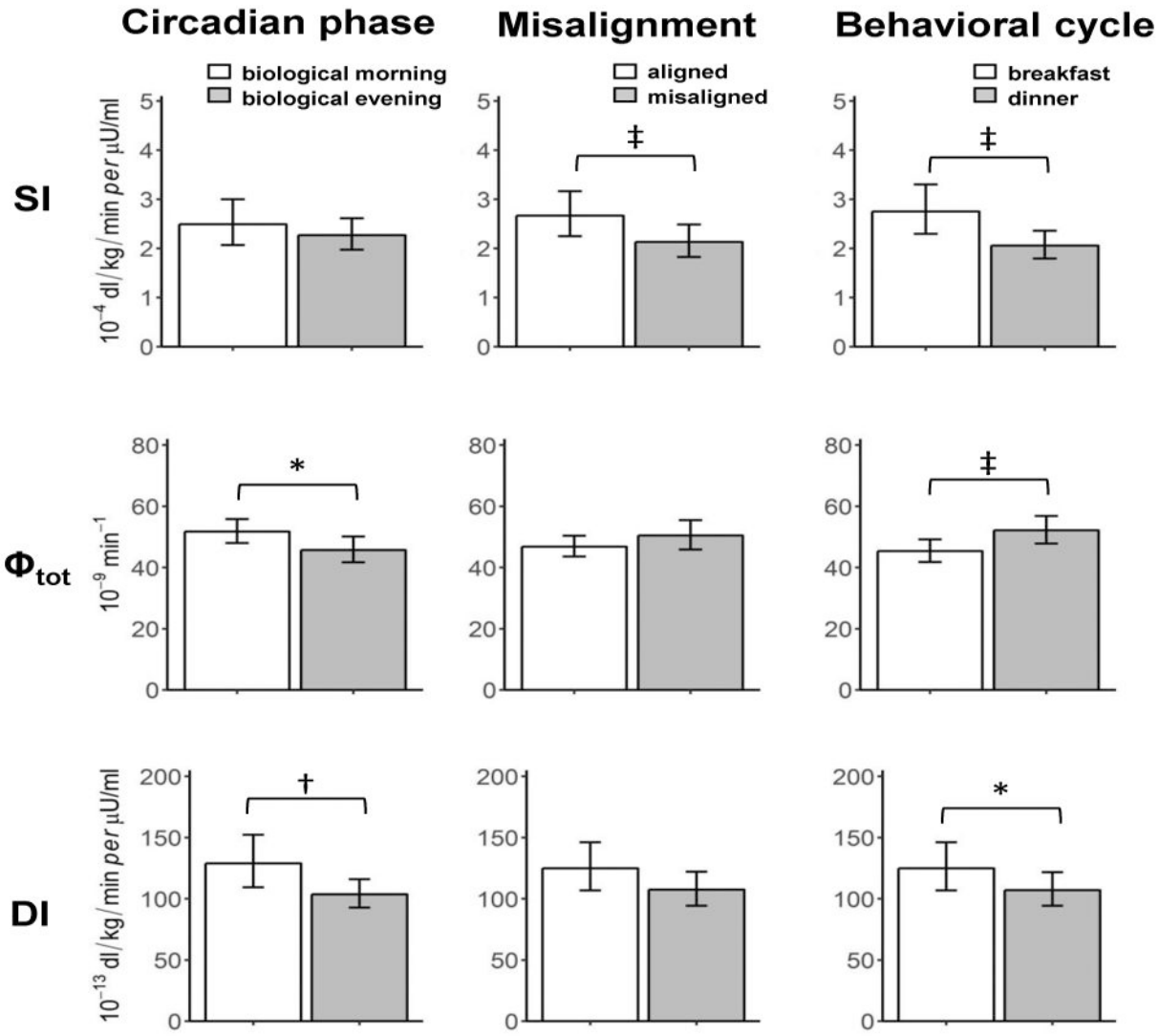

Figure 1.

Effects of the circadian phase (left), circadian misalignment (central), and behavioral cycle (right) on indices of insulin sensitivity (SI, top), total β-cell responsivity (Φ_{tot}, middle), and Disposition index (DI, bottom). Data are reported as geometric means (95% CI). *P<0.05, †P<0.01, ‡P<0.001.

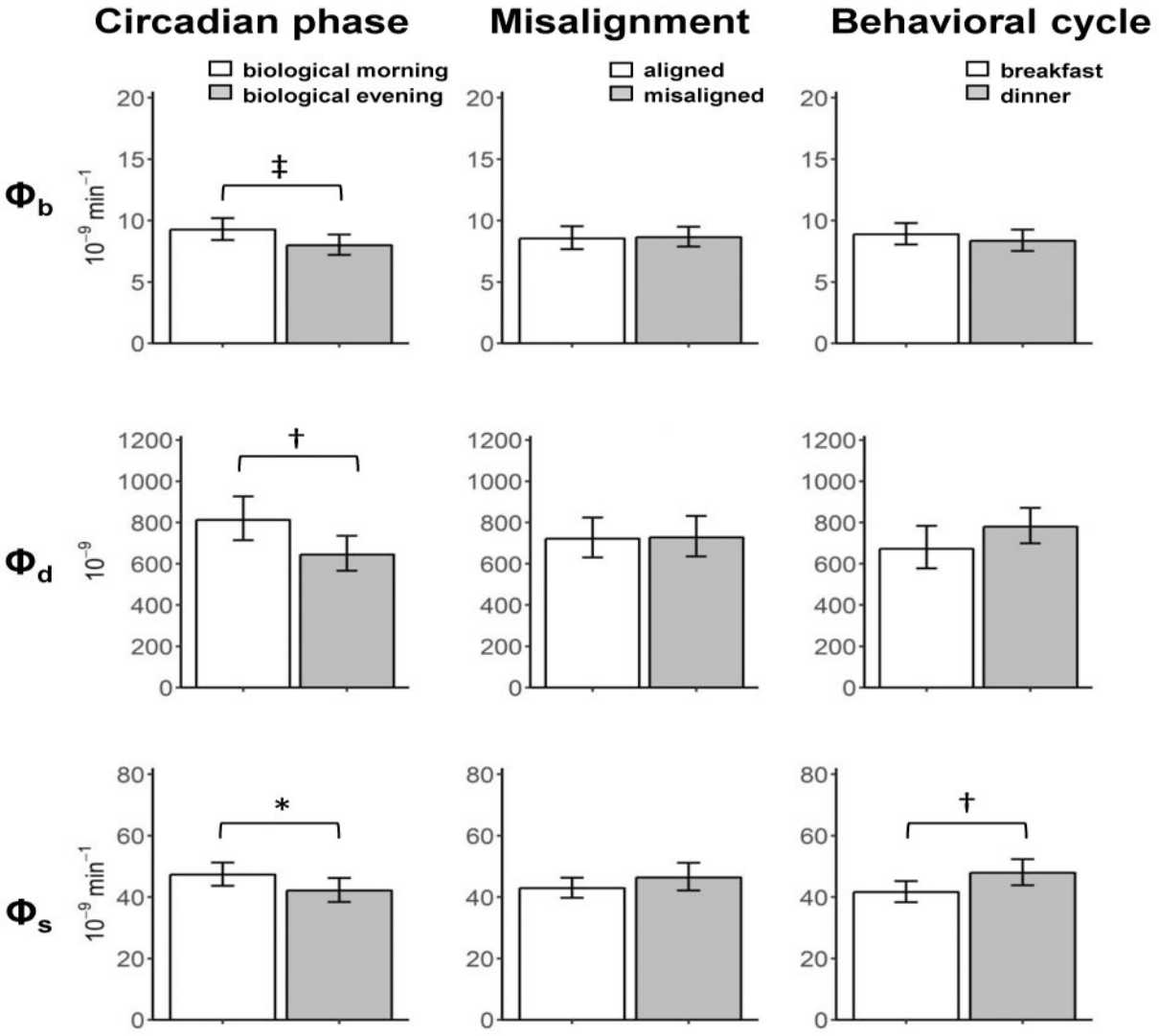

Figure 2.

Effects of the circadian phase (left), circadian misalignment (central), and behavioral cycle (right) on indices of basal β-cell function (Φ_b, top), dynamic β-cell responsivity (Φ_d, middle), and static β-cell responsivity (Φ_s, bottom). Data are reported as geometric means (95% CI). *P<0.05, †P<0.01, ‡P<0.001.