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Postprandial Metabolic Profiles Following Meals and Snacks Eaten during Simulated Night and Day Shift Work

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ABSTRACT

Shift workers are known to have an increased risk of developing cardiovascular disease (CVD) compared with day workers. An important factor contributing to this increased risk could be the increased incidence of postprandial metabolic risk factors for CVD among shift workers, as a consequence of the maladaptation of endogenous circadian rhythms to abrupt changes in shift times. We have previously shown that both simulated and real shift workers showed relatively impaired glucose and lipid tolerance if a single test meal was consumed between 00:00–02:00 h (night shift) compared with 12:00–14:00 h (day shift). The objective of the present study was to extend these observations to compare the cumulative metabolic effect of consecutive snacks/meals, as might normally be consumed throughout a period of night or day shift work. In a randomized crossover study, eight healthy nonobese men (20–33 yrs, BMI 20–25 kg/m^2) consumed a combination of two meals and a snack on two occasions following a standardized prestudy meal, simulating night and day shift working (total energy 2500 kcal: 40% fat, 50% carbohydrate, 10% protein). Meals were consumed at 01:00/13:00 h and 07:00/19:00 h, and the snack at 04:00/16:00 h. Blood was taken after

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an overnight fast, and for 8 h following the first meal on each occasion, for the measurement of glucose, insulin, triacylglycerol (TAG), and nonesterified fatty acids (NEFA). RM-ANOVA (factors time and shift) showed a significant effect of shift for plasma TAG, with higher levels on simulated night compared to day shift ($p < 0.05$). There was a trend toward an effect of shift for plasma glucose, with higher plasma glucose at night ($p = 0.08$), and there was a time-shift interaction for plasma insulin levels ($p < 0.01$). NEFA levels were unaffected by shift. Inspection of the area under the plasma response curve (AUC) following each meal and snack revealed that the differences in lipid tolerance occurred throughout the study, with greatest differences occurring following the mid-shift snack. In contrast, glucose tolerance was relatively impaired following the first night-time meal, with no differences observed following the second meal. Plasma insulin levels were significantly lower following the first meal ($p < 0.05$), but significantly higher following the second meal ($p < 0.01$) on the simulated night shift. These findings confirm our previous observations of raised postprandial TAG and glucose at night, and show that sequential meal ingestion has a more pronounced effect on subsequent lipid than carbohydrate tolerance.

Key Words: Shift work; Circadian rhythm; Cardiovascular disease; Triacylglycerol; Insulin resistance; Occupational medicine.

INTRODUCTION

Approximately one in five of the workforce in the United Kingdom is engaged in some form of shift work. Health problems within this population are therefore of economic and industrial importance. Shift work is associated with a number of negative effects, including disturbed sleep and gastrointestinal disorders, but the well-documented increased risk of cardiovascular disease (CVD) is a particular cause for concern (Kawachi et al., 1996; Knutsson, 2004; Knutsson et al.,1986; Kristensen, 1989). In the recent Helsinki heart study, the relative risk of CVD amongst shift workers compared with day workers was 1.4 after adjustment for lifestyle factors, blood pressure, and fasting lipid levels (Tenkanen et al., 1997). The causes are undoubtedly multifactorial, but a major factor is likely to be maladaptation of endogenous circadian rhythms to abrupt changes in shift times.

The use of strategies to hasten circadian adaptation to night shifts results in improved sleep and performance (Bjorvatn et al., 1999; Eastman and Martin, 1999), but there is, in contrast, a paucity of data concerning time-dependent metabolic and hormonal responses to food. Insulin sensitivity exhibits diurnal variation with a nadir of sensitivity at night (Morgan et al., 1999; Van Cauter et al., 1989). This diurnal variation in insulin sensitivity and its consequences for the metabolic handling of a meal is particularly relevant to shift workers' increased risk of CVD because of the association of insulin resistance with increased risk of CVD (Reaven, 1988).

Night and shift work causes workers to eat at different clock times than day workers (see for example: Costa (1997), Pasqua and Moreno (2004), Reinberg (1983), Waterhouse et al. (2003)). We have previously shown in both simulated shift-work studies in controlled laboratory conditions (Ribeiro et al., 1998) and in real shift workers (Lund et al., 2001) that circulating glucose and triacyglycerol (TAG)

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levels are significantly higher following a single meal eaten at night compared with one eaten during the daytime, a finding consistent with increased insulin resistance at night. TAG is an independent risk factor for coronary heart disease (Hokanson and Austin, 1996); thus, meals consumed at night when an individual has not adapted to nighttime working may contribute to the increased CVD risk of shift workers.

During a night shift, an individual is likely to consume more than one meal or snack. The purpose of this study, therefore, was to extend our previous observations to compare the cumulative metabolic effects of sequential meals and snacks as would normally be consumed during a typical period of day or night shift working. Eight-hour daytime and night-time metabolic profiles for glucose, insulin, TAG, and nonesterified fatty acids (NEFA) were therefore compared following consumption of two meals and a snack.

METHODS

Participants

Eight lean, healthy male participants, aged 20–33 yrs with a Body Mass Index (BMI) between 20–25 kg/m^2 were recruited from students and staff at the University of Surrey. Participants were all non- or light smokers (<10 cigarettes/day) and not taking any medication, with the exception of mild analgesics. A medical history and standard haematological screening were done prior to inclusion in the study. During the three days prior to each study day, participants were requested to maintain a regular sleep–wake cycle, rising at 07:00 h and retiring to bed at 23:00 h. They were asked to abstain from caffeine and alcohol consumption and avoid strenuous exercise on the day before and on each study day. In addition, urine was collected every 4 h (every 8 h when subjects were asleep) for 48 h to measure the circadian rhythm marker 6-sulphatoxymelatonin (aMT6s), on the day prior to and on each study day. Written consent was obtained from each participant after a full explanation of the purpose and nature of all procedures used and ethical approval for the study was obtained from the University of Surrey Advisory Committee on Ethics. The protocol and its conduct adhered to the good practice guidelines of the Journal (Touitou et al., 2004).

Protocol

The study was a two-way randomized crossover design. Participants were studied on two occasions, on a simulated day or night shift. They were provided with all their meals throughout the study days. These consisted of a combination of meals and snacks typical of a normal Western diet, at prescribed intervals (total energy intake/study day, 2500 kcal; percentage of energy as fat 40%). The timing and composition of the meals and snacks are shown in Table 1. No food apart from the provided meals and snacks were consumed during each study day, but participants were allowed free access to water. Participants consumed two meals and a snack over the course of the simulated day or night shift (composition and timing shown in

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Table 1. Timing, energy, and macronutrient content of the test meals.

	Time (h)		Energy	Macronutrient content (% total energy)		
	Day shift	Night shift	(kcal)	CHO	Fat	Protein
Prestudy meal	07:00	19:00	750	51	38	11
Prestudy snack	10:00	22:00	243	48	47	5
Meal 1	13:00	01:00	760	55	34	11
Snack	16:00	04:00	243	48	47	5
Meal 2	19:00	07:00	750	51	38	11

Table 1). The food intake of the participants was controlled for 6 h before each study day/night, with a standardized meal and snack (Table 1). Prior to that time, participants were free to follow their usual diets. Venous blood was collected 30 min after each meal and at 1 h intervals for 8 h following the first meal on each occasion (day shift: 12:00–20:00 h; night shift: 00:00–08:00 h) from an anticubital forearm vein. Plasma was separated immediately by centrifugation, aliquoted, and stored at −20°C until analysis. Both the simulated day and night shifts were carried out under similar lighting conditions (natural daylight was excluded on the simulated day shift). The two legs of the study were conducted 7–14 days apart from each other. A single fasting blood sample was also collected on a separate occasion, within 1 week of the study. Plasma glucose, TAG, and NEFA (reagents obtained from Randox Laboratories, Co. Antrim, UK) were measured by standard automated enzymatic spectrophotometric methods. The interassay coefficients of variation were less than 5%. Plasma immunoreactive insulin was measured by an immuno-chemiluminometric assay (MLT, Cardiff, UK). Urinary aMT6s was measured by radioimmunoassay (Aldous and Arendt, 1988). The interassay coefficients of variation were less than 10% for these two assays. For all analyses, samples obtained following the daytime and nighttime test meals from a single subject were measured in the same assay.

Data and Statistical Analysis

The aMT6s data underwent a computerized cosinor analysis, using a program developed by Dr. D. S. Minors at the University of Manchester to ascertain calculated peak times of melatonin secretion. The cosinor approach was used to analyze the time series data for circadian rhythmicity by fit of a single cosine curve using the method least-squares to derive the parameters of mesor (a 24 h time series mean), amplitude (one-half the peak-to-trough variation), and acrophase (peak time referenced to local midnight) of the best waveform approximation.

Postprandial hormone and metabolite responses were estimated as the total area under the response curve (AUC), calculated using the trapezoidal rule.

Hormonal and metabolic data were compared by repeated measures ANOVA followed by the Tukey-Kramer multiple comparisons test to determine significant differences at particular time points, and acrophase data were compared by paired

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t-test, using the Statistica statistical package (Statsoft, Tulsa, Oklahoma, USA). Mean ± SD values are presented unless otherwise stated, and p values of <0.05 were considered to be statistically significant.

RESULTS

The body clock status of the participants, as assessed by measurement of the circadian rhythm marker aMT6s, was not significantly different between the day and nighttime legs of the study. Their mean acrophase time for aMT6s was 4.2 ± 0.27 h (SEM). Moreover, there were also no significant differences between the day and nighttime legs in the amplitudes or mesors.

Fasting TAG levels were 0.66 ± 0.3 mmol/L. Plasma TAG levels following the meals are shown in Figure 1 and Table 2. Repeated measures ANOVA (factors time and shift) over the entire study period showed significantly raised plasma TAG on the simulated night shift compared to day shift ($p < 0.05$). Inspection of the areas under the curve (Table 2) showed the greatest differences between day and night-shift TAG levels occurred during the mid-portion of study period, following the snack.

Fasting glucose levels were 5.1 ± 0.6 mmol/L. Plasma glucose levels following the meals are shown in Figure 2 and Table 2. Repeated measures ANOVA (factors time and shift) over the entire study period revealed a trend ($p = 0.08$) toward higher glucose levels on the simulated night compared to day shift. Inspection of the areas under the curve (Table 2) showed significantly greater integrated glucose levels in the

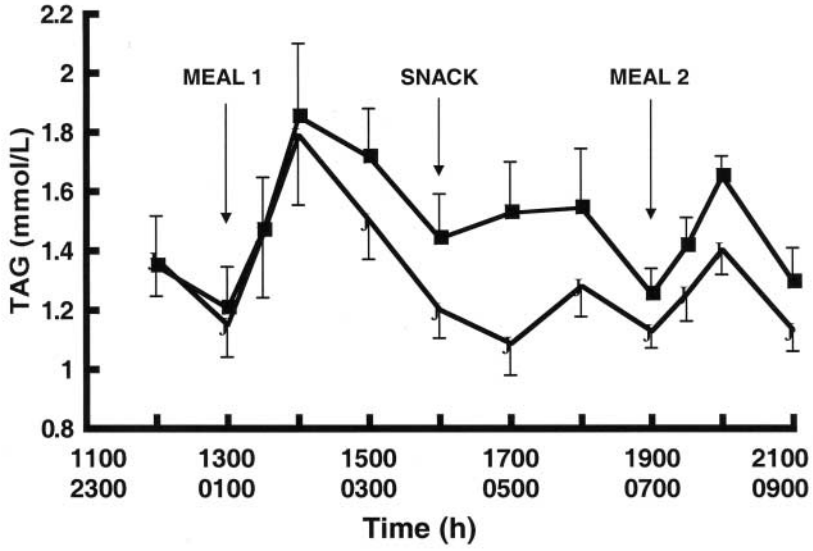

Figure 1. Plasma triacylglyceride levels following meals and snacks consumed during either the day (●) or night (■). Figures are mean ± SEM, $n = 8$.

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Table 2. Areas under the postprandial response curve for meals and snacks eaten either during the day or the night. Values are means (SEM), $n = 8$.

	Total AUC (0–8 h)		AUC 1st meal (0–3 h)		AUC snack (3–6 h)		AUC 2nd meal (6–8 h)	
	Night	Day	Night	Day	Night	Day	Night	Day
TAG	12.2[a]	10.5[a]	4.8	4.5	4.4[a]	3.5[a]	2.9	2.5
(mmol/l.h)	(0.9)	(0.6)	(0.5)	(0.4)	(0.4)	(0.3)	(0.1)	(0.1)
Glucose	44.5	41.7	17.2[a]	15.3[a]	16.5	15.5	10.8	10.9
(mmol/l.h)	(1.8)	(1.4)	(0.6)	(0.6)	(0.8)	(0.4)	(0.5)	(0.5)
Insulin	1375	1484	550[a]	699[a]	384	452	440[b]	334[b]
(pmol/l.h)	(128)	(128)	(64)	(65)	(45)	(63)	(41)	(24)
NEFA	2.8	3.1	1.2	1.3	0.9	1.1	0.7	0.7
(mmol/l.h)	(0.2)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)

[a,b]Denotes significant difference between day and night: [a]$p < 0.05$; [b]$p < 0.01$.

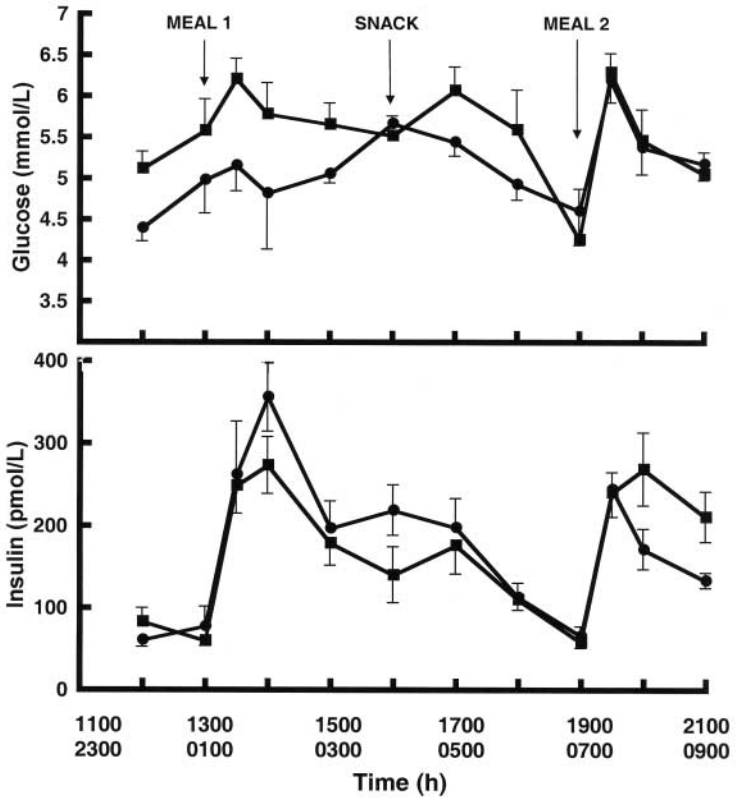

Figure 2. Plasma glucose and insulin levels following meals and snacks consumed during either the day (●) or night (■). Figures are mean ± SEM, $n = 8$.

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early part of the study period, following the first meal ($p < 0.05$), but no differences in the latter part of the study period.

Fasting insulin levels were 52 ± 10 pmol/L. Plasma insulin levels following the meals are shown in Figure 2 and Table 2. Repeated measures ANOVA (factors time and shift) over the entire study period showed no significant effect of shift on insulin levels but a significant shift by time interaction ($p < 0.01$). Inspection of the areas under the curve (Table 2) revealed a significantly smaller integrated insulin response on the simulated night shift following the first meal ($p < 0.05$), but a significantly larger insulin response following the second meal in the latter part of the study period ($p < 0.01$).

Fasting NEFA levels were $0.97 + 0.2$ pmol/L. Repeated measures ANOVA (factors time and shift) over the entire study period for plasma NEFA showed significant differences in 0 NEFA levels with time ($p < 0.01$), but no differences with shift, or shift by time interaction. NEFA levels fell following the first meal on both day and night shifts; thereafter, only small and inconsistent changes with time occurred. There were no significant shift differences in the areas under the plasma NEFA curve following any of the meals.

DISCUSSION

The study was designed to compare the metabolic effects of meals on simulated day and night shifts under conditions where participants were not adapted to night-shift work. Body clock status, as assessed by measurement of the circadian rhythm marker aMT6s, was not significantly different between the day and nighttime legs of the study; the mean acrophase time was typical of that normally seen in a comparably aged persons living in the UK (Lund et al., 2001) adhering to a consistent and normal sleep/wake cycle. Although adaptation to night shift can occur in some isolated environments (Gibbs et al., 2002; Lund et al., 2001), adaptation of the circadian clock to the night shift in fast rotating shift schedules is rare (Costa, 1997). The circadian status of the participants on the night-shift leg of the study was, therefore, representative of the beginning of the period of night-shift work and most likely typical for the complete duration of some night-shift patterns.

Plasma TAG levels were elevated following meals consumed during the simulated night shift relative to the day shift, throughout the entire time period studied. This pattern confirms previous meal studies in simulated (Hampton et al., 1996; Holmbäck et al., 2002; Romon et al., 1997) and real (Lund et al., 2001) shift work, and it is consistent with the observation that mean plasma TAG levels under constant routine conditions are highest around 04:00 h (Morgan et al., 1998). The mechanism behind this effect relates to the effects of insulin on lipid metabolism. Insulin activates lipoprotein lipase (LPL), a key regulatory enzyme governing circulating TAG uptake into cells. We have previously demonstrated 24 h variation in LPL activity, with lower activity during the night than daytime, which is consistent with a relative insulin resistance at night (Asaradnam et al., 2002). The greatest relative elevation in plasma TAG occurred following the mid-shift snack (04:00–06:00 h) and was predominantly a consequence of consumption of the 01:00/13:00 h meal, although mean TAG levels remained higher after the nighttime

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consumption of food, until the end of the study at 09:00 h. Sequential fatty meals were associated with an earlier postprandial rise in TAG than single meals, with mean peak levels being attained at 120 min, in contrast to some 4–5 h postprandially as in our previous single meal studies. There is evidence that this early postprandial circulating TAG is derived from fat consumed with the previous meal (Fielding et al., 1996).

Plasma glucose levels were also elevated following the 01:00 h meal compared with the 13:00 h meal, confirming previous studies. In contrast to TAG, glucose tolerance following the second meal at 07:00/19:00 h was unaffected by time of day. Reduced glucose utilization, decreased insulin sensitivity, and inappropriately low insulin secretion are probably all involved in causing relative glucose intolerance at night (Van Cauter et al., 1997). There is a sleep-related component governing glucose tolerance in addition to a circadian component (Morgan et al., 1998; Van Cauter et al., 1997), and chronic sleep debt has a deleterious effect upon glucose tolerance (Spiegel et al., 1999). However, the metabolic recovery in glucose tolerance that occurred at the end of the simulated night shift implies that the circadian component predominates in the short term, as recovery occurred in spite of the participants being acutely sleep deprived, from being kept awake during the simulated night shift.

Plasma insulin levels were lower following the nighttime meal at 01:00 h compared with the equivalent day-time meal. This is in contrast with previous findings (Hampton et al., 1996; Knutsson et al., 2002; Lund et al., 2001; Ribeiro et al., 1998). However, other studies have failed to show higher insulin levels following nighttime meals (Holmbäck et al., 2003), or an inconsistent rise in plasma insulin levels at night despite raised glucose levels (Shapiro et al., 1988; Van Cauter et al., 1992). The failure to observe a compensatory rise in plasma insulin at night in response to a raised glucose has been shown to be partly due to a diminished sensitivity of the pancreatic β cell to glucose (Lee et al., 1992). The magnitude of this effect may be related to the macronutrient composition of the meals or the participants' previous diets, accounting for the observed differences in the literature. In the present study, we did not standardize energy or macronutrient intake for more than 6 h before the day and nighttime studies. This led to differences in energy intakes for the preceding 24 h between the day and nighttime legs, because of participants' normal sleep patterns. The reason this protocol was adopted was that it is more representative of a free-living shift worker. After the second meal at 07:00/19:00 h, insulin levels were higher when the meal was taken in the morning than evening, consistent with the lower insulin response observed at night. It thus appears that the recovery of glucose tolerance observed at the end of the simulated night shift is achieved by increased insulin secretion.

Raised NEFA levels are considered to be a risk factor for coronary heart disease (Frayn, 1998). We failed to find any influence of shift on postprandial NEFA levels in this study. A 24 h rhythm in plasma NEFA levels has been previously observed; in diurnally active persons, highest levels occur in the morning, decreasing throughout the day, with a second increase at night (Reaven, 1988). However, these findings were likely to be more closely related to patterns of food intake than to any endogenous circadian rhythmicity.

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Time-dependent variations in the hormonal and metabolic responses to food are well established (Morgan et al., 2003). The 24 h variation in insulin sensitivity and its consequences for the metabolic handling of a meal is particularly relevant to increased risk of shift workers to CVD because of the association of insulin resistance with increased risk of CVD (Reaven, 1988). It is associated with a cluster of metabolic interrelated abnormalities known as Syndrome X or metabolic syndrome. These abnormalities typically include varying degrees of glucose intolerance, dyslipidaemia, raised blood pressure, and truncal obesity, all risk factors for cardiovascular disease. If shift workers repeatedly consume meals at night, during the circadian phase of maximal insulin insensitivity, the cumulative postprandial effects may predispose individuals to display other abnormalities of the metabolic syndrome. While dietary energy and macronutrient intake is generally not affected by shift work, a temporal redistribution of food intake does occur (Lennernas et al., 1995). Night-shift workers are also more dependent upon snacks than day shift workers (Waterhouse et al., 2003). Moreover, an increased incidence of dyslipidaemia, hypertension, and truncal obesity has been reported in shift workers (Nakamura et al., 1997; Romon et al., 1992). The findings of a more recent study show shift workers have a higher prevalence of metabolic syndrome (Karlsson et al., 2001). The present study demonstrates a persistence of relative lipid intolerance throughout the night, although metabolic recovery of glucose tolerance occurred at the end of the simulated night shift, suggesting that restriction of dietary fat intake throughout the night would be beneficial in night-shift workers who are not adapted to nighttime working.

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