Hormonal changes in satisfied and dissatisfied shift workers across a shift cycle

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There is ample evidence that shift work, including night work, increases the risk for the development of both psychological (8, 45) and physiological health problems (23). The most well-established links exist between shift work and increased risk for cardiovascular heart disease (11, 49), gastrointestinal disorders (55), and clinical sleep disorders (23), with the risk increasing with the number of years exposed to shift work (25). It is reasonable to believe that the main cause of increased morbidity is the disruption of sleep-wake behavior and the resulting conflict with the circadian system. There is, however, a limited knowledge of the mechanisms behind disease susceptibility in shift workers.

Sleep appears to be a central problem, and polysomnographic studies have shown that sleep in shift workers is often displaced and/or shortened, particularly in connection with morning and night shifts (3, 24, 51, 53). Several laboratory studies have confirmed that such sleep disturbances alter the regulation of several hormones (63) [for example, cortisol, prolactin, and growth hormone in both shift and night workers (46, 63–66) and other populations (38, 47, 56)]. A few studies have been carried out in the work place (12, 28, 50, 54), and they have shown that working nights or being on call are not only related to increased ACTH and epinephrine release but also to reduced levels of testosterone. However, further studies on shift workers are needed because most of these studies are limited by their small sample sizes.

Although the main negative effects of shift work are well documented, it is obvious that not all individuals are equally affected: whereas some individuals develop problems, others thrive (6, 16, 22, 39). A number of individual properties have been tested as causes of the variation in tolerance [for example, diurnal type, circadian amplitude, sleep flexibility, and age] but with poor success (1, 34). Possibly, a more fruitful approach might be to look for differences between groups with high and low tolerance for shift work. This might yield knowledge about the mechanism behind problems in shift work.

In an attempt to understand more about the variation in tolerance of shift work, we compared individuals satisfied with shift work with those dissatisfied. The results showed that the latter accumulated problems with sleep and fatigue across a work period (even though they did not differ with respect to objective sleep variables) (6a). It appeared that some individuals develop problems, others thrive (6, 16, 22, 39). A number of individual properties have been tested as causes of the variation in tolerance [for example, diurnal type, circadian amplitude, sleep flexibility, and age] but with poor success (1, 34). Possibly, a more fruitful approach might be to look for differences between groups with high and low tolerance for shift work. This might yield knowledge about the mechanism behind problems in shift work.

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focuses on the endocrine differences between satisfied and dissatisfied shift workers. The variables for comparison were selected from key indicators of catabolic (cortisol) and anabolic activity (testosterone). In addition, prolactin was measured because of its sensitivity to sleep and stress (35, 46, 58) and also for its importance as a regulator of immune function and cellular osmosis (17).

Because intolerance to shift work may be related to the accumulation of problems across a shift cycle, the present study involved blood samples at the start and end of a shift cycle. To maximize shift load, workers with a particularly difficult shift schedule with two consecutive quick returns were selected. This extremely rapidly rotating and advancing schedule involved a night shift, 8 h off, an afternoon shift, 9 h off, a morning shift, and 55 h off. This was repeated seven times and was followed by 8 days off.

METHODS

First, 317 of 368 full-time shift workers were invited to participate as control room operators, shift engineers, machinists, and shift supervisors at a paper and pulp factory filled out a questionnaire in 1995 in which they rated their “satisfaction towards their work hours” (1 = very dissatisfied, 5 = very satisfied). These ratings were used to divide the shift workers into two groups who were either satisfied or dissatisfied with their shift schedule. The shift workers with a rating of 3 or lower were considered “dissatisfied,” whereas those rating 5 were considered “satisfied.”

Next, 62 of the 269 male shift workers were invited to participate in two health examinations where blood was to be drawn. Twenty were excluded (chose not to participate in the blood drawing procedure, changed to day work, changed employment, or were on long-time sick leave). Thus the groups in the present study were 42 men, of which 22 were satisfied [with a mean age of 44 ± 2 (SE) yr] and 20 dissatisfied (41 ± 2 yr). Relatively few shift workers were dissatisfied with their work hours (only 8% of all shift workers rated 2 or lower). The resulting difference in satisfaction between satisfied and dissatisfied shift workers became 5.0 ± 0 vs. 2.4 ± 0.2.

All participants gave their informed consent before inclusion in the study. They were instructed to adhere to their normal behavior during the entire shift cycle and were not paid to participate. The study was approved by the local ethical committee of the Karolinska Institutet.

The shift cycle (comprising 35 days and 5 shift teams) was extremely rapidly rotating and included 7 work periods and 1 wk off. The shift schedule was as follows

\[ N A M + N A M + N A M + N A M + N A M + N A M \]

where \( N \) is night shift (2100–0600), \( A \) is afternoon shift (1400–2100), \( M \) is morning shift (0600–1400), + is day off, and underlined text is weekend. “Work period” consisted of three shifts during 4 days (\( N A M + \)), with only 8 h off between the night and afternoon shift and 9 h off between the afternoon and morning shift. Each shift worker was examined twice, once during the first of seven work periods and once during the last work period. The shift system had been in use for >20 yr when the study was carried out.

The study also included the Karolinska Sleep Questionnaire (4), the Karolinska Sleep Diary (2), a wake diary, actigraphy, two health examinations, and performance tests. The main bulk of these data will be presented elsewhere, but some variables will be used here for correlations with hormone variables. The questionnaire contained questions about background, sleep characteristics, the work situation, social factors, health symptoms (including sleep items), and well-being.

The questions concerning sleep problems were “snoring,” “exhausted upon awakening,” and the indexes were “disturbed sleep” (containing “difficulties falling asleep,” “repeated awakenings,” “disturbed sleep,” “premature awakening”) and “sleepiness problems” (containing “sleepiness during work/leisure,” “involuntary falling asleep at work,” “involuntary falling asleep during leisure time,” and “have to fight against sleep to stay awake”); all used the response alternatives 1 = always, 2 = mostly/several times a week, 3 = sometimes/several times per month, 4 = seldom, 5 = never (during the last 6 mo). Other items were “diurnal-type” (1 = profound evening type, 4 = profound morning type (49)), “habitual sleep need” (hours and minutes), and “sufficient sleep?” (1 = no, far from sufficient, 5 = yes, definitely sufficient). In addition, the questionnaire included questions of whether sleep was disturbed in connection with day sleep (after the night shift) or before the morning shift; the questions concerned whether sleep was “disturbed” or “insufficient” and the feeling of “not being well rested” (scales ranging from 1 = never to 5 = always). The shift workers also rated their need of recovery after a work period (how many nights needed to recover, 1 = one sleep, 2 = two sleeps, 3 = 3 or more sleep periods) and as well as their general health (1 = very poor, 5 = very good).

The two groups did not differ on most background variables age [ANOVA, \( F = 1.0, P = 0.33 \)], degrees of freedom (df) = 1,41], being married or cohabiting [satisfied vs. dissatisfied, 82 h, 55%, \( \chi^2 (1) = 3.5, P = 0.06 \)], proportion with children under the age of 7 [18 vs. 20%, \( \chi^2 (1) = 0.0, P = 0.88 \)], proportion smoking [14 vs. 20%, \( \chi^2 (1) = 0.3, P = 0.58 \)], taking regular medication [at least once a week, 14 vs. 26%, \( \chi^2 (1) = 1.0, P = 0.31 \)], body mass index (BMI; 26 ± 1 vs. 26 ± 1 kg/m², \( F = 0.2, P = 0.62, \text{df} = 1,41 \)], diurnal type (2.6 ± 0.2 vs. 2.2 ± 0.3, \( F = 2.4, P = 0.13, \text{df} = 1,41 \)) ease overcoming sleepiness (3.4 ± 0.1 vs. 3.2 ± 0.2, 1–4 = very easy, \( F = 1.8, P = 0.19, \text{df} = 1,41 \)). However, dissatisfied shift workers had a higher habitual sleep need (8.1 ± 0.3 vs. 7.0 ± 0.2 h, \( F = 10, P < 0.01, \text{df} = 1,41 \)) and lower sleep flexibility than satisfied shift workers (2.4 ± 0.2 vs. 3.4 ± 0.1, 1–4 = very flexible, \( F = 24.1, P < 0.0001, \text{df} = 1,41 \)).

Fasting blood samples were obtained between 0700 and 0900 on the morning shift during the first and the last (7th) work period (from September 1996 to late spring 1997). The samples were centrifuged within 2 h, and serum was directly frozen and sent for analysis (of cortisol, prolactin, and testosterone) to Nova Medical (Calab, Sweden). Serum cortisol and serum testosterone were analyzed by using ELISA (Boehringer Mannheim) with a fully automatic immunooassay system (ES 700, Boehringer Mannheim). The total intra- and interassay coefficient of variability (CV) was <8.0% for cortisol and <5.0% for testosterone. Prolactin was analyzed with a two-site chemiluminometric immunoassay with an automated chemiluminescence system (model ACS:180, Ciba Corning Diagnostic, Medfield, MA). The total CV% was <8.0%.

The data were analyzed by using repeated-measures ANOVA with one between-group and one within-group factor. The main factors were “satisfaction with the shift schedule” (satisfied vs. dissatisfied) and “work period” (the 1st vs. the 7th work period in the shift sequence). For the ANOVA,
the significance levels were set to 0.05, but also trends are reported \((P < 0.10)\) in the tables because this is the first study evaluating hormonal changes across a shift schedule. Correlations were computed between the hormones (the mean for both samples) and ratings of background data, sleep characteristics, and sleep/sleepiness problems from the questionnaire. For the correlation analysis, a more restricted \(P\) value \((0.01)\) was used to minimize the risk of making type I errors. Here, trends were set to the 0.05 level and will only be reported in the tables. A set of multiple stepwise regression analyses was conducted to find the best predictors of morning levels of the hormones. All variables significantly related \((<0.05)\) to a hormone were included as predictors.

**RESULTS**

Table 1 shows that the only significant difference between satisfied and dissatisfied shift workers was the lower level of testosterone in the latter group. There was also a tendency toward higher prolactin levels among dissatisfied shift workers. For the two groups combined, the levels of morning cortisol decreased significantly across the shift cycle. There was no significant interaction between satisfaction and work period.

A two-tailed correlation analysis was conducted to evaluate whether testosterone and cortisol were correlated. The resulting correlation for the first work period was \(r = 0.34\) \((P < 0.05, n = 42)\) and for the last work period was \(r = 0.39\) \((P < 0.01, n = 42)\). In addition, the correlation between the start and the end of the shift cycle was \(r = 0.79\) \((P < 0.001, n = 42)\) for testosterone, \(r = 0.57\) \((P < 0.001, n = 42)\) for cortisol, and \(r = 0.80\) \((P < 0.001, n = 42)\) for prolactin.

Morning levels (mean for both samples) of testosterone and cortisol were significantly related to several background variables, sleep characteristics, and sleep/sleepiness problems from the questionnaire (Table 2). High testosterone levels were related to satisfaction with the shift schedule, a low habitual sleep need, fewer sleepiness problems, and a faster recovery after each work period. Moreover, high testosterone levels were also related to sufficiency of sleep and to being well rested after day sleep, and to less disturbed sleep before morning shifts. High morning cortisol was associated with having a morning personality and positive ratings of being well rested and sufficiency of sleep before morning shifts. The correlation between “morningness” and cortisol was strong \((r = 0.40, P < 0.01, n = 42; r = 0.43, P < 0.01, n = 42)\), for the first and the last work period, respectively). Morning levels of prolactin were not significantly related to any of the questionnaire variables. In addition, the change of cortisol across the shift cycle was not related to any of the other variables studied.

In the stepwise multiple regression analyses, the sole predictor of morning testosterone levels was the need for recovery \(\left[n = \text{days that a subject needed after each work period; adjusted } R^2 (R^2_{\text{adj}}) = 0.21, \beta = -0.48, F = 12.0, P < 0.001\right]\). The exclusion of

### Table 1. Hormone levels for satisfied and dissatisfied shift workers during their first and last work period in the shift schedule

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Satisfied</th>
<th>Dissatisfied</th>
<th>F Values</th>
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<tbody>
<tr>
<td></td>
<td>1st</td>
<td>7th</td>
<td>1st</td>
</tr>
<tr>
<td>Cortisol, nmol/l</td>
<td>402 ± 23</td>
<td>381 ± 24</td>
<td>389 ± 23</td>
</tr>
<tr>
<td>Testosterone, nmol/l</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Prolactine, μg/l</td>
<td>5.5 ± 0.7</td>
<td>5.2 ± 0.6</td>
<td>7.5 ± 0.8</td>
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<table>
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<th></th>
<th>Mean ± SE</th>
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| 1st, First work period; 7th, last work period; S X W, the interaction between satisfaction and work period. Degrees of freedom range between 1.40 and 1.41. Significance levels are \(\dagger P < 0.05, \ddagger P < 0.01, \dagger P < 0.10\). Trends are \(\dagger P < 0.10\).
recovery need resulted in general sleepiness problems becoming the best (and only) predictor of testosterone levels \( R^2_{adj} = 0.17, \beta = 0.43, F = 8.9, P < 0.01 \). After the exclusion also of general sleepiness, the best and only predictor became “not well rested” after the day sleep interjected between the night and the afternoon shift \( R^2_{adj} = 0.16, \beta = 0.43, F = 8.5, P < 0.01 \). Testosterone was not significantly related to smoking \((R = -0.09, P = 0.55, n = 42)\), BMI, or age, and forcing age into the regression analysis did not alter the outcome.

The best predictors of morning cortisol were diurnal type (being a morning type, \( R^2_{adj} = 0.22, \beta = 0.35, F = 5.8 \)) and ratings of sufficiency of sleep before the morning shift. The latter added another 7% of explained variance \((\beta = 0.33, F = 4.9; \text{total model } R^2_{adj} = 0.29, F = 9.3, P < 0.001)\). When diurnal type was excluded, the ratings of sufficient sleep before morning shifts became the only predictor of cortisol levels \( R^2_{adj} = 0.20, \beta = 0.48, F = 11.0, P < 0.01 \).

Figure 1 illustrates some of the observed relations by using recovery days, sleepiness problems, and diurnal type to classify the individuals. Figure 1, A and B, shows how shift workers needing more than one recovery day after a work period and those with more sleepiness problems had reduced morning testosterone. Figure 1C shows that evening types had lower levels of morning cortisol than morning types.

**DISCUSSION**

Dissatisfied shift workers had lower morning testosterone than satisfied ones, but the two groups did not significantly differ with respect to levels of cortisol or prolactin. Low testosterone levels were, furthermore, associated with a great sleep need, disturbed sleep, and sleepiness problems. The results seem to link an important endocrine variable to the main problems in shift workers, disturbed sleep/alertness. We have, in the same subjects, previously shown that dissatisfaction with the shift schedule was related to an accumulation of problems with sleep and sleepiness across the work period (6a). This may explain their increased need for recovery after the work period, and the latter was the best predictor of testosterone levels in the present study. It seems likely that suppressed testosterone represents a weakened anabolic capacity and, obviously, increased sensitivity to quick returns.

The lower testosterone in dissatisfied shift workers may be interpreted with four different perspectives: sleep loss, stress, depression, and lack of control. The disturbed night sleep-testosterone connection is supported by the observations that night work and being on call at night suppresses morning testosterone (12, 54) and that more severe sleep disturbances (long-term sleep deprivation, sleep fragmentation, and sleep apnea) in the laboratory suppress or disrupt testosterone regulation, as well as increase sleepiness (5, 29, 30).

The degree of testosterone suppression is related to the degree of sleep disruption (43). In addition, short sleep (3 h) is less disruptive for testosterone than no sleep at all (37). Moreover, low testosterone levels are associated with fatigue (30), and exogenous testosterone has been shown to improve alertness and well-being in hypogonadal patients (14, 33).

The second explanatory pathway, stress due to shift work, is suggested by a number of studies demonstrating reduced testosterone in response to physiological and mental stressors (60, 69). Critical illness causes a profound and acute decrease of testosterone (67). The
combination of extreme physical and mental stress in military survival training radically suppresses testosterone (35). Also, work-related stress, as in the case of a reorganization and threat of unemployment, may decrease testosterone (19). The effects were reversible, because testosterone increased when the stressor was withdrawn. On the other hand, if stress were the mediator of the reduced testosterone in the present study, one would have expected increased cortisol levels, but this did not occur. In fact, cortisol was positively correlated to testosterone, which makes stress, at least in the sense of increased hypothalamus-pituitary-adrenal (HPA) axis activity, less likely as an explanation of the reduced testosterone in dissatisfied shift workers. However, it is still possible that a subtle overactivation of the HPA axis exists in dissatisfied shift workers.

A third possibility derives from the finding that major depression is associated with suppressed testosterone levels (44, 69), with the suppression of testosterone being related to an increased activation of the HPA axis. However, despite a higher level of anxiety/depressive symptoms in those who were dissatisfied with their shift schedule, it was only modest and did not reach any clinical criteria (6a). In addition, and as stated earlier, there were no signs of increased cortisol in the dissatisfied group, which would be expected in depressed subjects.

Another explanatory possibility concerns the consequences of control. Both primate and human studies have shown that being unsuccessful (being dominated, losing a competition, social defeat) reduces testosterone (7, 10, 27, 32). In contrast, winning a competition increases testosterone, with the increase being even greater if the winner is in a positive mood or if he evaluates his own performance highly (10, 32). Thus it is possible that dissatisfied shift workers may experience their situation as hopeless, resulting in a suppression of testosterone. Indeed, it has been demonstrated that the testosterone response works as a feedback regulator reinforcing, or weakening, the hormonal pattern that stimulated the behavior in the first place (14, 69). It could therefore be debated whether it is the stressor itself or if it is how one experiences the outcome that suppresses testosterone. As a consequence, testosterone levels may instead reflect how well someone is coping. However, such an adaptive response mechanism, which also would reflect “fitness” and social status (29), would not explain the fact that low testosterone levels are related to disturbed sleep.

In the light of our testosterone results, even though our data cannot verify causal relationships, it seems reasonable to hypothesize that the low levels of testosterone may be due to disturbed sleep and/or a high sleep need, which, in turn, may result in more sleepiness and a greater need for recovery after a work period and, as a consequence of these problems, dissatisfaction with the shift schedule.

The only significant change across the shift cycle was the lowering of morning levels of cortisol on the last morning shift in the shift cycle. The reduced morning cortisol could either reflect some form of downregulation of the HPA axis (68) or, alternatively, an alteration of the circadian rhythm at the end of the shift period. It seems possible that the reduced morning cortisol may reflect a downregulation or adaptation to long-term stress, particularly as sustained stress may downregulate cortisol (40, 68). It is thought that the chronic adaptation to long-term stress is due to increased sensitivity of the feedback mechanisms. On the other hand, a change of the circadian rhythm is also possible, but it is difficult to control for because our data are based on single morning samples. In addition, satisfaction with the shift schedule was not related to diurnal type or to cortisol levels, despite the fact that testosterone was positively related to both cortisol and satisfaction. Hence, the relation between cortisol and testosterone may be independent of satisfaction. Moreover, the fact that satisfaction was not related to diurnal type contradicts some earlier studies (8, 23), but it is probably due to the characteristics of the shift system. In fact, no circadian adaptation could be expected, or even desired, in such an extremely rapidly rotating shift system (19). The only observation related to diurnal type was the higher morning cortisol and fewer sleep problems before morning shifts in morning types.

Besides its more well known importance for reproduction, prolactin is also involved in the regulation of immune function, osmoregulation, and angiogenesis (17). It is mainly released during sleep, but it is also, to a lesser extent, under circadian influence (42, 46, 62). Several studies have shown that many stressors alter prolactin (13, 18, 19, 35, 36, 58), but negative findings have also been reported (31). In the present study, neither working an entire shift schedule nor being dissatisfied (and hence also having low testosterone and poorer sleep quality and more sleepiness problems) was significantly related to morning levels of prolactin in the present study; only a trend toward higher prolactin levels was found in the dissatisfied group. This is perhaps contradictory because sleep is a major regulator of prolactin release. On the other hand, the unchanged prolactin levels resemble findings of normal prolactin levels in depressed patients and the elderly (48, 57). Alternatively, and despite some of the previous findings, morning levels of prolactin may be of minor biological importance, particularly as most prolactin is released during the night and after an initial peak after awakening declines drastically. Instead, it might be more relevant to measure prolactin during sleep. Nonetheless, as prolactin is known to influence testosterone levels (41), we cannot conclude that the individual differences in morning testosterone are independent of prolactin.

The interpretations of the present result are necessarily affected by several aspects of the design. First, many factors besides satisfaction may affect testosterone, for example, age, time of day, general health, BMI, sexual/physical activity, genetic factors, smoking, alcohol use, and intake of other drugs (9, 15, 59). In the present sample, there were no differences between satisfied and dissatisfied shift workers with respect to
age, BMI, smoking, physical activity, or intake of medicines, and none of these variables was significantly correlated to testosterone. Thus it was not necessary to control for these variables in the regression analysis. No control for alcohol was made because of the problems of obtaining accurate information and the conflicting results of a link between alcohol and testosterone (15, 21, 69).

Second, one needs to consider circadian changes. To control for such effects, all blood samples were taken between 0700 and 0900 in the morning. At this time, testosterone is released in a stable manner and is well representative of an individual’s testosterone levels (12, 58, 66). A single morning sample can also indicate whether cortisol is unusually low, reflecting a suppression (40) or phase shift of its rhythm. Diurnal type was not related to satisfaction and could, hence, not explain any differences in testosterone. Each individual was, in addition, sampled twice, with a high intraindividual correlation between the first and the last work period, for all measured hormones. This suggests that a single morning sample well reflects the individual levels.

A further consideration concerns the fact that we may not have obtained an optimal baseline measure of the hormones, a common problem in many field studies. As a consequence, we cannot determine whether the difference in testosterone represented an acute suppression or whether it was a more chronic down-regulation of the hypothalamus-pituarity-gonalad system. Because all morning shifts were preceded by a night, and an afternoon, shift, it was not feasible to get morning samples that were preceded by days off. In addition, it was not possible, for practical reasons, to sample blood outside the work place. However, the fact that the individual testosterone levels were highly stable across the seven work periods ($r = 0.79$) suggests a more chronic suppression.

In conclusion, the results clearly suggest that dissatisfaction with the shift system is related to lower testosterone levels and that the latter are related to disturbed sleep/wakefulness and increased need for sleep and recovery. In addition, working an entire shift cycle was related to a decrease of morning cortisol, which may relate to an adaptation to long-term stress. Furthermore, it is argued that low testosterone levels and disturbed sleep might be key factors for developing shift intolerance, mainly by reducing the capacity to recover from shift work. However, studies with more ambitious sampling procedures, and with an experimental approach, are needed to shed light on the mechanisms involved in intolerance to shift work.

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**REFERENCES**

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HORMONAL CHANGES IN SHIFT WORKERS


