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Authors
Kuhlwein, E
Hauger, R L
Irwin, M R

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Abnormal Nocturnal Melatonin Secretion and Disordered Sleep in Abstinent Alcoholics

Eva Kühlwein*
Richard L. Hauger, MD**
Michael R. Irwin, MD*[1]

*Cousins Center for Psychoneuroimmunonology,
University of California, Los Angeles (UCLA), Neuropsychiatric Institute, and
**Department of Psychiatry, University of California, San Diego

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Corresponding address:
Michael Irwin, M.D.
Norman Cousins Professor
Department of Psychiatry and Biobehavioral Sciences
Cousins Center for Psychoneuroimmunology
University of California, Los Angeles
300 UCLA Medical Plaza, Suite 3-109
Los Angeles, California 90095-7057
Tel: 310 825 8281
FAX: 310 794 9247
mirwin1@ucla.edu

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Abstract

Background: Alcoholic patients show prominent disturbance of EEG sleep with difficulties in the onset and maintenance of sleep. Given the role of melatonin in the regulation of the sleep-wake cycle, this study examines the relationship between nocturnal expression of melatonin and sleep in alcoholics as compared to controls.

Methods: Alcoholic patients (n=11) and comparison controls (n=10) underwent all-night polysomnography and serial blood sampling every 30 minutes from 22:00h to 6:30h for measurement of circulating levels of melatonin and cortisol.

Results: Coupled with prolonged sleep latency, alcoholics showed lower levels of melatonin during the early part of the night and a delay in the onset of the nocturnal plateau or peak value of melatonin as compared to controls. The nocturnal delay of melatonin correlated with prolonged sleep latency. Circulating levels of cortisol were lower during the early part of the night and higher in the late part of night in the alcoholics as compared to the controls.

Conclusions: A delay in the nocturnal rise of melatonin may contribute to disordered sleep in chronic alcoholics, with implications for the use of melatonin in the treatment of insomnia in recovering alcoholics.

Introduction

Sleep disturbance is one of the most common complaints of recovering alcoholics. Even after abstinence of weeks to months, alcoholic patients complain of difficulty falling asleep and maintaining their sleep (Gillin et al 1994; Brower et al 1998; Drummond et al 1998). Polysomonographic sleep studies confirm these subjective complaints with evidence of prolonged sleep latency and reduced sleep efficiency (Williams et al 1981; Snyder et al 1985; Brower et al 1998; Irwin et al 2000). Disordered sleep is thought to contribute to daytime fatigue and sleepiness in alcoholics, and has been found to predict those recovering alcoholics who are at greatest risk to relapse (Gillin et al 1994; Brower et al 1998; Drummond et al 1998; Foster et al 1999). The mechanisms that account for abnormal sleep in recovering alcoholics are poorly understood.

Sleep-wake activity is driven in part by circadian dependent processes. Melatonin is thought to have effects on sleep by resetting the internal biological clock (Brzezinski, 1997), whereas circulating concentrations of cortisol are not reliably associated with sleep measures of continuity (Friess et al 1995). Indeed, early evening administration of melatonin has been found to decrease sleep latency and increase sleep efficiency in the elderly (Zhdanova et al 2001) and in patients with primary insomnia (Garfinkel et al 1995; Haimov et al 1995; Zhdanova et al 1995; Girardin et al 1998) but have no effects on measures of sleep architecture or REM sleep (Zhdanova et al 2001). Likewise, in older adults and psychiatric populations such as depressed patients, melatonin onset and/or peak values are altered in association with disturbances of sleep continuity (Nair et al 1984; Beck-Friis et al 1985; Kennedy et al 1989; Dijk et al 1999).

In alcoholics, the relationship between melatonin and disordered sleep is not known. Prior reports have suggested that melatonin levels are abnormal in alcoholics, yet conclusions are

limited by the study of patients who had severe liver disease, were actively drinking, and/or had secondary depression, or relying on a single plasma or urinary level rather than a profile of secretion. (Moss et al 1986; Majumdar et al 1987; Murialdo et al 1991; Wetterberg et al 1992; Fonzi et al 1994; Wikner et al 1995; Schmitz et al 1996).

This study evaluated the nocturnal secretion of two circadian dependent hormones, melatonin and cortisol, along with EEG measures of sleep continuity in chronic alcoholics who were abstinent for three weeks or longer. Alcoholics are hypothesized to show abnormalities of sleep continuity that will be associated with decreases and/or delays in the nocturnal secretion of melatonin, but not with cortisol.

Methods and Materials

Subject selection

A total of 33 men were evaluated for inclusion in this study: 16 controls and 17 alcoholic patients. Both control and alcoholic subjects were African-American, as prior studies had found that African American alcoholics show more severe abnormalities of EEG sleep as compared to Euro-American alcoholics (Irwin et al 2000). Alcoholic patients underwent withdrawal prior to admission to the Alcohol and Drug Treatment Program (ADTP) at the Veterans Affairs San Diego Healthcare System (VASDHS). Alcoholic subjects were clinically hospitalized in the ADTP for 2 weeks before and during testing in the current research study. Non-patient control subjects were age-matched ($\pm$ 5 years) and had socio-demographic characteristics similar to the alcoholic patients. After complete description of the study to the subjects, written informed consent was obtained using procedures approved by the Human Subjects Protection Committees at University of California, San Diego, VASDHS, and University of California, Los Angeles.

Research diagnoses of control and alcoholic patients were made following the administration of a semi-structured interview developed by the multi-site Collaborative Study on the Genetics of Alcoholism (Bucholz et al 1994). Control subjects fulfilled DSM-IV criteria for Never Mentally Ill (APA, 1994). Alcoholic patients fulfilled DSM-IV criteria for alcohol dependence in the absence of major pre-existing or concomitant psychiatric disorders (Schuckit, 1985; Association, 1994) including secondary depression that may confound interpretation of EEG abnormalities in alcoholics (Gillin et al 1990). Severity of depressive symptoms was evaluated using the 17-item Hamilton Rating Scale - Depression (HRS-D) on the day prior to beginning the sleep protocol (Endicott, 1981).

All subjects were in good health as determined by medical history and laboratory screening blood tests. None of the alcoholics had histories of overt alcohol-related liver disease such as jaundice and/or oesophageal varices. Prior to entry into the study, medication histories were obtained and three alcoholics and two controls were excluded as they were taking medications known to alter sleep wake activity (e.g., β-blockers, non-steroidal anti-inflammatory agents, steroids). All alcoholic participants were free of psychotropic medications for greater than two weeks prior to EEG sleep assessment.

Alcoholics were studied after acute and subacute withdrawal symptoms had resolved; i.e. after at least two weeks of abstinence while hospitalized (Table 1). Nursing observations and random urine toxin screens were used to confirm abstinence during treatment. Urine toxin screens were also obtained in controls upon entry into the study and at random intervals during the sleep protocol resulting in the exclusion of one control.

Two weeks before entry into the study, sleep-wake activity diaries were obtained in alcoholics and controls. All subjects were sleeping regularly between 22:00 hours (h) and 7:00 h

with similar average bed- and wake times in the controls (23:50 h / 6:40 h) and alcoholics (23:12 h / 6:36 h). In addition, these habitual sleep wake activity patterns obtained prior to study were similar to the experimental night in which average bed- and wake times were 23:20 h / 6:30 h in the controls and 23:24 h / 6:36 in the alcoholics. Furthermore, both groups had exposure to outdoors light. In the two weeks prior to the experimental night, controls were living in the community and alcoholics had scheduled times outdoors throughout the clinical treatment day, attended community Alcoholics Anonymous meetings, or visited recovery homes or sober living environments in preparation for discharge from the ADTP.

Prior to the experimental night, subjects underwent an adaptation night in the sleep laboratory during which apneic episodes were assessed by means of overnight polysomnography along with measurement of nasal and oral airflow by end-tidal carbon dioxide detection and thermistry and oximetry for arterial oxyhemoglobin saturation. The cut-off criteria for sleep apnea was set at 15 events per hour in which an event was defined by a desaturation of 4% or greater for 10 seconds or greater. Nocturnal myoclonus was also recorded and scored according to procedures and criteria reviewed by (Guilleminault, 1982); myoclonus index was computed as the ratio nocturnal myoclonus to net sleep time in hours with a cut-off criteria for nocturnal myoclonus set at 12 movements per hour with an arousal defined as 3 seconds of EEG arousal. Following this sleep screening night, three additional controls were excluded; one due to sleep apnea or two due to nocturnal myoclonus. Finally, in three alcoholics, blood sampling was incomplete due to clotting of the IV line. Thus, of the entry sample, 6 controls were ineligible (n=2, medication; n=1, positive urine toxin screen; n=3, sleep disorder), and 6 alcoholics were excluded (n=3, medication; n=3 incomplete blood sampling); the study analyses included 10 controls and 11 alcoholics.

Procedures

Subjects were admitted to the sleep laboratory affiliated with the UCSD Mental Health Clinical Research Center (C. Gillin, Director) and the General Clinical Research Center (M. Ziegler, Director) for two nights of study. The first night was an adaptation night for screening of sleep apnea and nocturnal myoclonus. The second night was for experimental assessment of sleep and the nocturnal secretion of melatonin and cortisol. Between the two nights, alcoholics returned to the ADTP, and controls were permitted to return to the community. For each night, subjects were admitted to the sleep laboratory between 20.00 and 21.00 h. Subjects then readied for sleep and had electrodes placed for EEG, electro-oculography, and submental electromyography recordings. During the experiment night between 20.30 and 21.30 h, an IV catheter was inserted into a forearm vein. The first blood sample was obtained after 30 minutes while subjects rested in a supine horizontal position. As noted above, lights were turned off at about 23:20 h and subjects were awakened at about 6.40 h after the last blood draw; alcoholics returned to the ongoing clinical treatment and controls were discharged from the MH-CRC or GCRC affiliated sleep laboratory.

For blood sampling, the IV catheter was connected to a long, thin plastic tube that enabled blood collection from an adjacent room without disturbing the subject's sleep. During blood sampling, 1000 ml continuous heparinized isotonic saline was infused. Blood was sampled every 30 minutes beginning at 22.00 h and continuing until 6.30 h. After the blood was obtained, it was delivered into EDTA-containing tubes and placed on ice and centrifuged for acquisition of plasma. All samples were then stored at -80^{o}C until assay.

Sleep EEG measures were obtained during continuous recordings between 22.00 h and 6.30 h. At bedtime (BT), lights are switched off to below 10 lux. Given evidence that alcohol

dependence is associated with disturbances of sleep continuity and that melatonin improves sleep latency and sleep efficiency, this study focused on EEG measures of sleep continuity. Sleep onset was defined as the first minute of stage 2 or rapid eye movement (REM) sleep followed by at least eight minutes of sleep in the next nine minutes. Sleep latency was the time between bedtime and sleep onset. Sleep efficiency was the ratio of total sleep time to the time in bed, multiplied by 100 (Irwin et al 2000). Visual scoring of the sleep EEG was done by raters blind to the subject's group status.

Assays

Liver function tests: As melatonin undergoes hepatic metabolism, liver function tests were obtained including aspartate aminotransferase (SGPT), alanine aminotransferase (SGOT), bilirubin, and alkaline phosphatase by previously described methods (Irwin et al 1990).

Melatonin and cortisol: Blood samples across the experimental night were available for assay of plasma concentrations of melatonin and cortisol in 21 subjects. Plasma concentrations of melatonin were measured by radioimmunoassay with kits manufactured by IBL Immuno-Biological Laboratories, Hamburg, Germany distributed by DiagnosTech International, Inc. The melatonin assay has a sensitivity of 2.5 pg/ml with an .intraassay coefficient of variation of approximately 8 % and an interassay coefficient of variation of approximately 15 % when performed within the standard range from 3.5 - 300 pg/ml. Plasma concentrations of cortisol were measured by radioimmunoassay with kits provided by Diagnostic Products Corporation, Los Angeles, CA. The assay has a sensitivity of 0.3 ug/dl with an intraassay coefficient of variation of approximately 4 % and an interassay coefficient of variation of approximately 6 % when performed within the standard range is from 0.5 - 50 ug/dl.

Statistical Analyses

The sociodemographic data, alcohol and drug consumption histories, liver function tests, and EEG sleep continuity measures were analyzed using independent t-tests or Chi-square tests as appropriate. The effect size was determined by using the f statistic. By criteria specified by Cohen (1988), effect sizes of 0.10 are considered small, 0.25 are considered medium and 0.40 or greater are considered to be moderate to large effects.

Analyses of melatonin and cortisol used a 2 (group: alcoholic, control) x 18 (nocturnal time points) repeated measures analyses of variance to evaluate main effects for group, time, and their interaction. To meet normality assumptions for these analyses, melatonin and cortisol values were log-transformed. Given the repeated measures design with blood sampling across the nocturnal period during uninterrupted sleep, some blood samples at individual time points were missing (<10 % of total number of samples). For missing time points, the mean of an individual's two adjacent values was substituted.

Onset of the nocturnal plateau/peak of melatonin was defined as the time point at which three consecutive values were similar and within the coefficient of variation for melatonin; during the nocturnal plateau, melatonin oscillated within the range of experimental variation without linear increases or decreases. Differences in plateau onset values between the two groups were compared by an independent t-test. Correlations were performed on all sleep measures that differed significantly between the groups. Nonparametric, Spearman correlations were performed to minimize the influence of extreme values; one data point for sleep latency fulfilled criteria for an outlier value exceeding 3 standard deviations above the sample mean and correlations were conducted with and without this outlier value.

Results

Table 1 summarizes the demographic characteristics, severity of depressive symptoms alcohol and drug consumption histories, and body mass index in the control and alcoholic groups. The two groups are similar in age and severity of depressive symptoms. However, the alcoholics had more drinking days per month, more drinks per drinking day, and more recent alcohol consumption than the controls. Body mass index was lower in alcoholics as compared to the controls. Values of the laboratory tests of the liver function did not differ between the alcoholics and controls (data not shown).

EEG measures of sleep continuity showed that alcoholics had prolonged sleep latency as compared to controls but had similar measures of total sleep time and sleep efficiency (Table 2).

As shown in Figure 1, the secretion of melatonin and cortisol changed differentially across the night in the alcoholic and control groups. For melatonin, there was a significant time effect *(F*=23.62, df=17,323*, p*<0.01) and a significant group x time interaction (*F*=3.56, df=17,323, *p*<0.01). The alcoholics showed decreases of melatonin during the early part of the night as compared to controls, with comparable values of melatonin during the late part of the night (Figure 1a). For cortisol, there was also a significant time effect (*F*=49.03, df=17,323, *p*<0.01) and group x time interaction (*F*=2.14, df=17,323, *p*<0.01) in which alcoholics had lower levels of cortisol during the early part of the night and higher levels of cortisol during the late night as compared to the controls (Figure 1b). Inclusion of body mass index as a covariate in these analyses did not alter the results.

Additional analyses were conducted to determine whether there were group differences in the time of nocturnal rise of melatonin or cortisol. Planned comparisons revealed that the onset of the nocturnal plateau of melatonin was significantly delayed in alcoholics as compared to

controls. On average, controls reached a nocturnal plateau of melatonin at 0.30 h $\pm$ 1.2 h whereas alcoholics did not achieve plateau of nocturnal melatonin until 1.95 h $\pm$ 1.16 h (t=-3.19, df=19, P<0.01; Figure 1a). No difference was found between the groups in the time of nocturnal increase of cortisol.

To evaluate whether the delay in the nocturnal secretion of melatonin was associated with the abnormalities of sleep continuity, correlational analyses were conducted between onset time of the melatonin plateau and sleep latency, the sleep continuity variable that differed between the alcoholics and controls. Prolonged sleep latency correlated with delay in onset of the nocturnal melatonin plateau with and without inclusion of the one high (>3 SD) outlier value for sleep latency (Spearman ρ= 0.50, p<0.02; Spearman ρ=0.49, p<0.03; Figure 2).

Discussion

Alcoholics show abnormal nocturnal secretion of the circadian-dependent hormones, melatonin and cortisol, as compared to controls. Moreover, alcoholics show a delay in the nocturnal rise of melatonin with lower levels during the early part of the night and a peak or plateau onset time that is over 90 minutes later than the controls. Coupled with the delay of nocturnal melatonin secretion, alcoholics show prolonged sleep latency that correlates with a later time of onset of the nocturnal plateau of melatonin.

The association between sleep latency and nocturnal melatonin secretion supports the notion that abnormally low melatonin values or a delay in the nocturnal release of this hormone might contribute to disordered sleep in alcoholics. It is also possible that delay of sleep onset leads to abnormal melatonin secretion, although this alternative is less likely since early night sleep deprivation does not alter the profile of melatonin secretion as compared to uninterrupted

sleep (Redwine et al 2000). Given other experimental evidence that evening administration of melatonin improves sleep quality in the elderly and primary insomniacs (Garfinkel et al 1995; Haimov et al 1995), the present study has important clinical implications relevant to the treatment of disordered sleep in alcoholics.

The present study extends prior observations of abnormal melatonin expression in alcohol dependence by obtaining repeated assessments of melatonin across the night in alcoholics who had undergone withdrawal and showed no evidence of liver disease or secondary psychiatric comorbidity. In contrast, previous investigations were limited to the study of alcoholics during active drinking or acute withdrawal and included patients who were heterogeneous in terms of age, ethnicity, and severity of liver disease (Williams et al 1981; Majumdar et al 1987; Murialdo et al 1991). In addition, the present population showed minimal depressive symptoms that would otherwise confound interpretation of differences in alcoholics. Abnormally low melatonin levels are found in major depression (Beck-Friis et al 1985) and correlate with depressive symptom severity in patients with anorexia nervosa (Kennedy et al 1989) and premenstrual dysphoric disorder (Parry et al 1997).

The nocturnal secretory profile of cortisol is also altered in recovering alcoholics as compared to controls with lower levels during the early part of the night and higher values during the late part of the night. While acute alcohol withdrawal is associated with hypercortisolemia, the persistence of this effect into abstinence is not well-established (Risher-Flowers et al 1988; Adinoff et al 1991). Indeed, Adinoff et al. found that plasma cortisol levels normalize following resolution of withdrawal, whereas Iranmanesh and colleagues (1989) suggested a delay of the cortisol acrophase that persisted into abstinence. The present study, limited to the nocturnal interval, did not identify a delay in the onset of the rise of cortisol during the night.

There are several limitations to the present study. First, the blood sampling interval was restricted to the nocturnal interval because the study was conducted within the clinical setting. Thus, inference about a shift in the circadian phase of the alcoholics can not be made without assessment of these hormones across the 24 hour period. In addition, onset of melatonin production, a more sensitive index of melatonin secretion, could not be determined as changes in melatonin concentrations were already underway at the time of the first blood sample at 22.00 h. Second, an African American population was exclusively studied because evidence suggests that African American alcoholics, as compared Euro-Americans, have increased severity of disordered sleep (Irwin et al 2000). Thus, it is not known whether differences of sleep and nocturnal neuroendocrine measures generalize to Euro-Americans. Third, the generalizability of the findings to active alcoholics in the community is limited as the present sample was studied after withdrawal from alcohol and during maintenance of abstinence in a controlled clinical setting. Nevertheless, it is important to note that by the use of this experimental design, differences in sleep and secretion of melatonin and cortisol can not be ascribed to a direct action of ethanol or to withdrawal effects. Fourth, the alcoholic group was limited to veteran men; conclusions about differences in alcohol dependent women or community groups cannot be made. Fifth, while the two groups reported similar habitual sleep-wake activity patterns in the two weeks prior to experimental study and had routine exposure to outdoors light, activity levels and light exposure during the day were not quantified in the two groups. Despite these limitations, this report represents an important step in an ongoing investigation to determine the mechanisms underlying disordered sleep in alcohol dependence in this understudied ethnic group. These data suggest that low levels of melatonin and/or a delay in its secretion to abnormal are associated with disordered sleep and increases of sleep latency in alcoholics.

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Table 1. Age, Education, Severity of Depressive Symptoms, Alcohol Consumption Histories and Body Mass Index in Control and Alcoholic Subjects

	Controls N=10 mean (SD)	**Alcoholics** N=11 mean (SD)	**Significance** (df=19)
Age (years)	38.2 (7.0)	39.4 (5.5)	*t*=0.43, *P*<0.67
Depressive symptoms (HRS-D Scores)	1.3 (1.8)	1.5 (1.6)	*t=-0.21, P*<0.84
Alcohol consumption (last 3 months)			
Drinking days/ month	1.4 (1.8)	27.1 (6.5)	***t*=-12.5, *P*<0.01**
Drinks/day	2.4 (5.5)	15.8 (16.2)	***t*=-2.59, *P*<0.02**
Days between last drink and experimental night	188.3 (186.4)	25.6 (6.4)	***t*= 2.76, *P*<0.02**
Body mass index	25.5 (4.2)	21.4 (2.0)	***t*=8.22, *P*<0.01**

Table 2. EEG Sleep Continuity in Control and Alcoholic Subjects

	Controls N=10 mean (SD)	**Alcoholics** N=11 mean (SD)	**Significance** (df=19)	**Effect Size**
Sleep Continuity				
Total sleep time (min)	364.3 (74.6)	333.1 (52.8)	*t*=1.11, *P*<0.28	f=0.07
Sleep efficiency (%)	85.8 (8.1)	77.3 (11.0)	*t*=2.01, *P*<0.06	f=0.46
Sleep latency (min)	6.4 (5.4)	33.1 (35.0)	***t*=-2.51, *P*<0.03**	**f=0.55**

Figure 1:

Differences in nocturnal secretion of melatonin (a) and cortisol (b) between abstinent chronic alcoholic and healthy men.

Figure 1 a shows a significant time effect (F=23.62, df=17,323, P<0.01) and time x group effect (F=3.56, df=17,323, P<0.01) for melatonin.

Figure 1a also shows a delay in time of onset of the melatonin plateau as illustrated by the broken circles and bracket (t=-3.19, df=19, P<0.01).

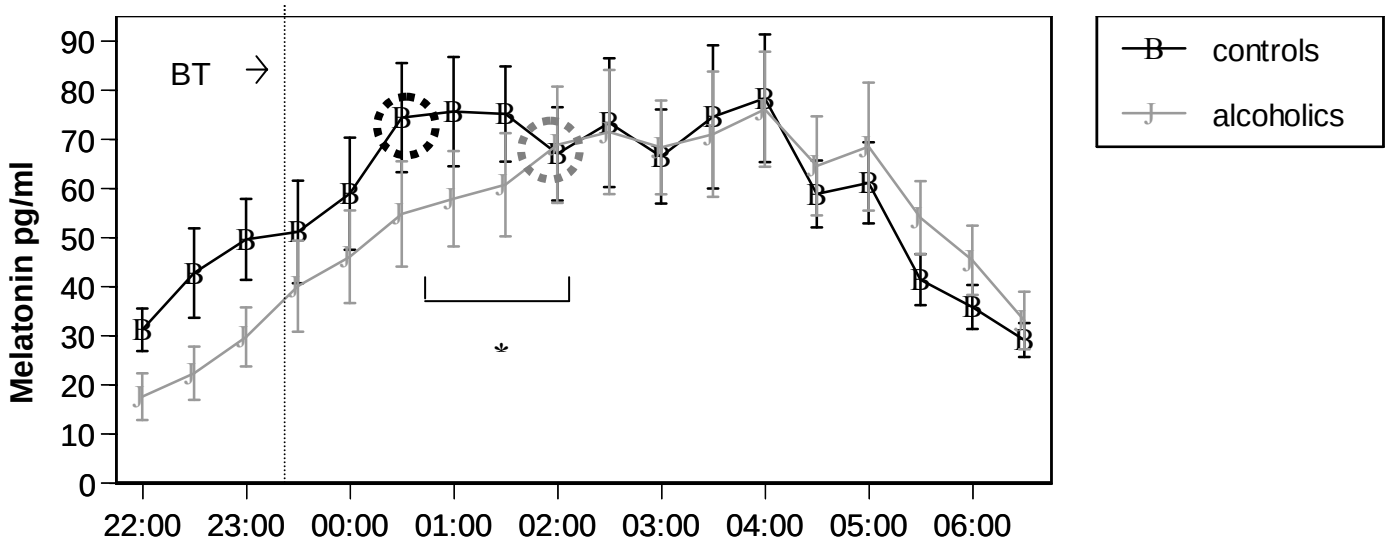
Figure 1 b shows a significant time effect (F=49.03, df=17,323, p<0.01) and time x group effect (F=2.14, df=17,323, p<0.01) for cortisol.

Figure 2:

Sleep latency correlated with time of onset of the nocturnal melatonin plateau in alcoholics and controls (Spearman ρ=0.50, df=21, P<0.02).

Figure 1

a


BT
Melatonin pg/ml
0
10
20
30
40
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60
70
80
90
22:00
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02:00
03:00
04:00
05:00
06:00
controls
alcoholics

b

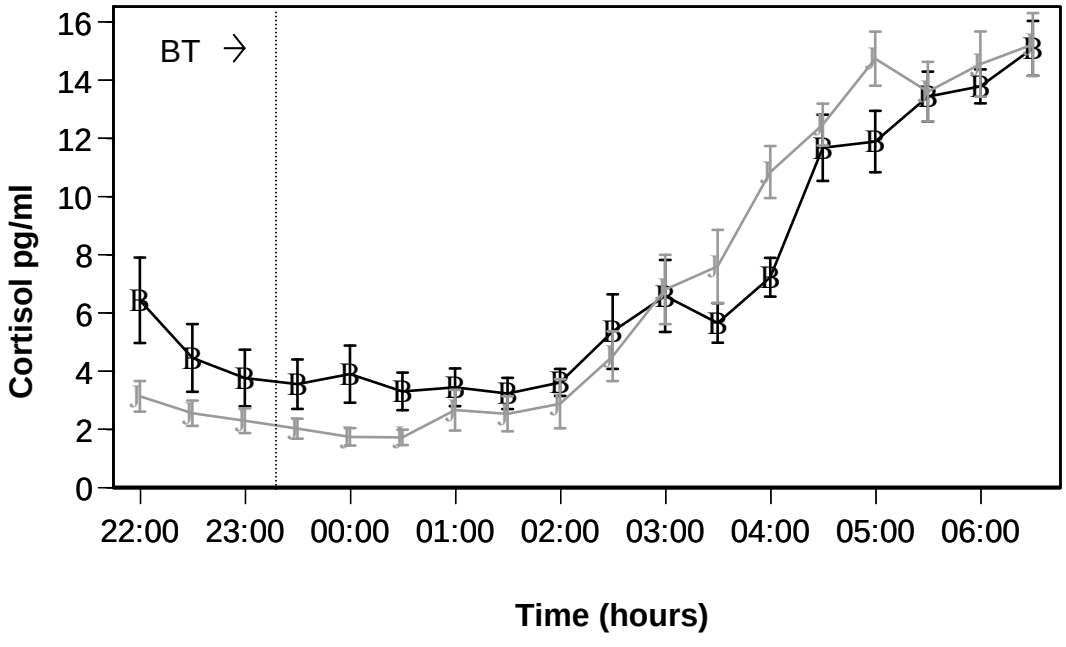
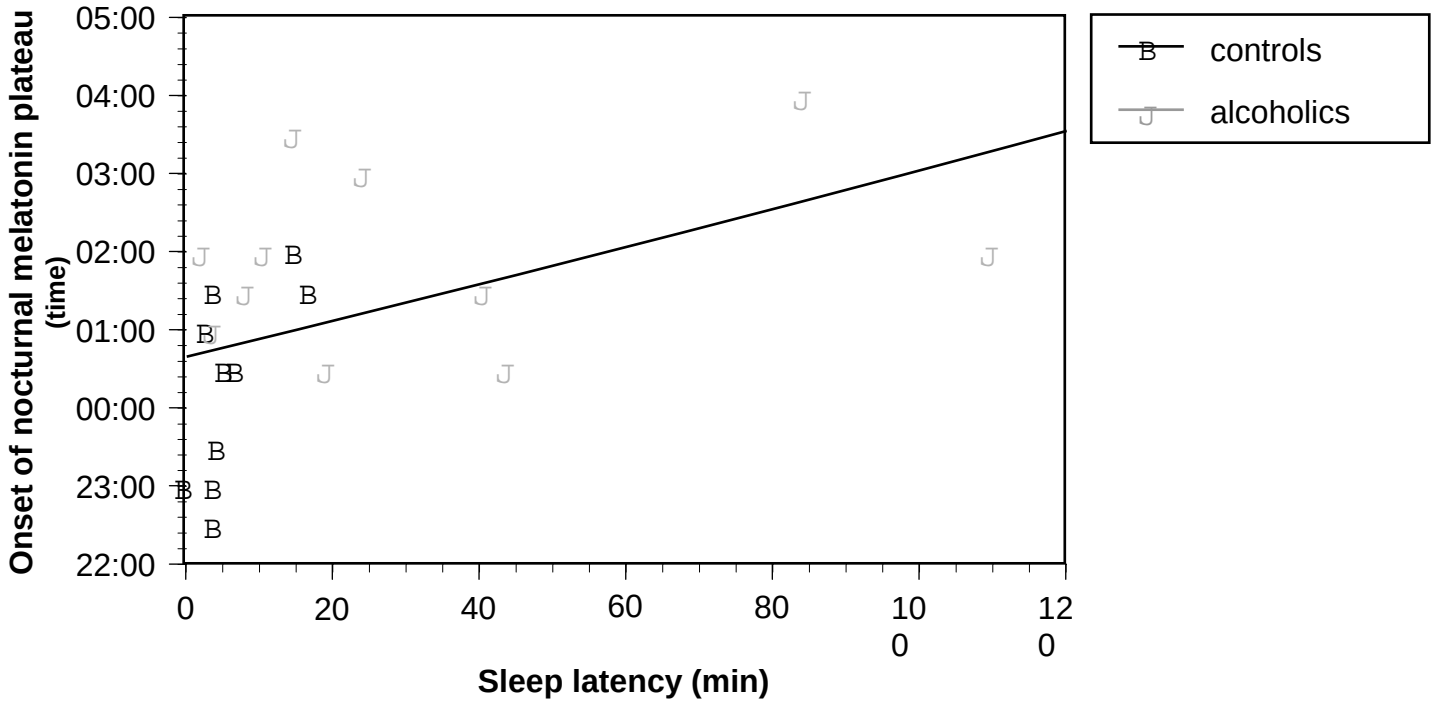

BT
Cortisol pg/ml
0
2
4
6
8
10
12
14
16
22:00
23:00
00:00
01:00
02:00
03:00
04:00
05:00
06:00
Time (hours)

Figure 2


Onset of nocturnal melatonin plateau (time)
05:00
04:00
03:00
02:00
01:00
00:00
23:00
22:00
0
20
40
60
80
100
120
Sleep latency (min)
controls
alcoholics