Circadian system rhythm disorders in aging and Alzheimer's disease. Role of changes in melatonin, suprachiasmatic nucleus and corticosteroids

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Influence of academic stress on circadian rest-activity and sleep-wake rhythm of female students

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The purpose of this study was to investigate the influence of academic stress on the circadian rest-activity and sleep-wake rhythm in female university students. Seven healthy female students (age: 22±1), screened for a variety of health and lifestyle factors, were studied for 21 days by actigraphy and perceived stress. The registration procedure is as following: 7 days of baseline condition, two weeks after baseline: 7 days record as before and 7 days record as during the examination. The examinations showed a significant increase in perceived stress scores. The present study demonstrates that academic stress increased the fragmentation of circadian rest-activity rhythm and induced a disruption in sleep-wake rhythm.

The circadian rhythm, a rhythm of approximately 24 hours, is present in many physiological and behavioral phenomena in most species. Examples are the rhythm in rest-activity, sleep-wakefulness, body temperature, and hormone levels. Circadian rhythms make it possible for the organism to adapt to its environment (16). This requires a circadian timing system that is able to synchronize the various circadian rhythms with each other and with the environmental light-dark cycle. The hypothalamic suprachiasmatic nucleus (SCN) is the predominant pacemaker of the mammalian brain that generates and controls circadian rhythms of various endocrine and behavioral processes (12). Stress, defined as physical or emotional influences that cause bodily or mental tension, results in a cascade of cardiovascular and endocrine responses (5,13). Academic stress is particularly strong in students, especially in China, where competition in the job market is very strong and where examinations are taken extremely seriously by most students. It was reported in the United States that academic stress produces a significant increase in medical students’ perceived stress scores, which is associated with an increase in adrenocorticotropic hormone (ACTH) levels during the day in the fall but, surprisingly, not in the spring (11). Other evidence also suggests that stress interferes with the maintenance of the circadian cortisol rhythm. The SCN generates and regulates the diurnal rhythm of glucocorticoid (GC) secretion. The high release of vasopressin (AVP) from the SCN

109
during the light period coincides precisely with the low levels of circulating corticosterone at this time of the day (8,15). The AVP neurons in the SCN are considered to be major inhibitors of the corticotropin-releasing hormone (CRH) neurons in the rat paraventricular nucleus (PVN) (1). Moreover, it was reported that the amount of AVP released within the SCN can vary widely, not only in accordance with the intrinsically regulated circadian rhythm of AVP but also in response to a physiologically relevant stressor (4). Few data are available about the relation between academic stress and circadian rest-activity and sleep rhythm (11). In the present study we investigate the influence of academic stress on circadian rhythm and the quality of sleep in Chinese college students.

A total of 7 healthy young female students, aged 22±1 (mean±SEM), completed the study protocol of academic stress. Subjects gave informed consent. None of them had a history of anxiety episodes or had received counselling or medication for any psychological disorders. Also, none of them reported recent illness or a history of sleep disorder. None were smokers and none used oral contraceptives. None of them were athletes or used chronic medication or recreational drugs. Their weight and blood pressure were within ±20% of ideal scales. All of them were living on campus and their activities were confined to the classroom or research center. Female students kept a 4-week and a 1-week sleep log, respectively, during the study, and all of them completed the Chinese version of Perceived Stress Questionnaire (PSQ) every week (9). Semester final examinations were given over one week. It is easy for students to lead a regular life during exam periods. Due to the special dorm management system in Chinese universities, there is no electricity after 11:30pm and students have to be in bed at that time. In the morning, the classes start at 8:00 am, and students must get up at about 7:30am. Students kept sleep diaries. Students were asked to record two times: time-in-bed and get-up-time. Students were also asked to record self-reported sleep-quality for every night in their sleep diaries. Personal information, such as weight, blood pressure, etc. is included in the sleep log too.

Actigraphy has been increasingly used in research fields, such as in research into sleep, circadian rhythm, aging, depression, hyperactivity and obesity (16). The actigraph is worn on the wrist like a watch. It continuously records and stores movement-induced acceleration. When the actigraph data are transferred to a computer after a period of recording, a clear circadian rhythm can be seen, and several variables calculated. (1). The Inter-daily Stability (IS) is the 24h value from the chi-square periodogram (19) normalized for the number of data, and gives an indication of the strength of coupling between the rest-activity rhythm and Zeitgebers. (2) Intradaily Variability (IV) gives an indication of the fragmentation of the rhythm, i.e. the frequency and extent of transitions between rest and activity, and is calculated as the ratio of the mean squares around the grand mean (overall variance) (17,19). (3) In addition to these measures describing
signal to noise ratios, a Relative Amplitude (RA) measure was calculated as follows: First, the 24-h pattern was determined by averaging over the 7 days of registration. Then from this pattern the average hourly movement duration was calculated for the uninterrupted least active 5-hour period (L5) and for the most active 10-hour period (M10). The RA was calculated by subtracting L5 from M10 and dividing the result by their sum (18,19). The Sleep Watch software (Cambridge Neurotechnology, Cambridge, UK), which compares favorably to other such packages (3) was used for estimation of the following sleep variables from actigraphic recordings: sleep time, sleep efficiency, wake bouts, total activity score and sleep onset latency.

The Wilcoxon matched paired test was used to evaluate changes of circadian rest-activity rhythm and sleep variables between baseline and exam in the same group. For the correlation between academic performance and sleep quality, the Spearman R test was performed. A p-value of < 0.05 was set for significance.

The mean and standard error mean of PSQ scores for the students were significantly different from 0.38±0.01 at baseline to 0.51±0.01 during examination (p=0.03). Academic stress significantly enhanced the mean level of IS from 0.49±0.03 to 0.66±0.02 (p=0.02). IV was increased from 1.16±0.03 at baseline to 1.61±0.07 during examination (p=0.03) and L5 was also enhanced from 367.43±51.03 to 509.71±89.71 (p=0.02). On the other hand, RA was significantly reduced from 0.95±0.01 at baseline to 0.92±0.01 during examination (p=0.03) and M10 from 17647.71±2229.27 to 13388.43±1880.50 (p=0.03).

With regard to sleep measures during the week (7 days) of examination, we observed shorter total sleep times (p=0.001), reduced sleep efficiency (p=0.003), more waking bouts after sleep onset (p=0.03), increased total activity score at night (p=0.001) and longer sleep onset latency (no significant difference) (Table 1).

No significant correlation was found between academic performance and sleep quality estimated by all of the above sleep variables. Traditionally Chinese students take exam scores very seriously. Therefore, exams are considered to be the strongest stressors during their university lives, as also appeared from the significant increase in college stu-

| Table 1 Sleep analysis for healthy young female students |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Total sleep time (min) | Sleep efficiency | Wake bouts | Total activity score | Sleep latency (min) |
| Baseline | 404.1 ± 8.5 | 86.5 ± 0.8 | 22.8 ± 0.9 | 3672.3 ± 408.9 | 22.9 ± 2.7 |
| Examination | 337.3 ± 12.3 | 82.8 ± 1.3 | 25.4 ± 0.8 | 4446.1 ± 254.3 | 23.8 ± 2.4 |
| P | < 0.001 | 0.003 | 0.03 | 0.03 | ns |
Students' perceived stress scores, which were associated with an increased fragmentation of circadian rest-activity rhythm and a disorder of sleep-wake rhythm. It is now widely accepted that among experiences of stress the release of GC by the adrenal glands is prominent (5,6). Hypersecretion of GC can promote the development of physiological and psychological dysfunction (6). On the basis of our current research it was proposed that GC exposure could affect the SCN vasopressin neurons, resulting in circadian rhythm disturbances. We recently found a clearly decreased amount of AVP mRNA in the SCN after prolonged GC exposure in a human post-mortem study (Liu et al., unpublished results). It has been reported that academic stress produces a dissociation among mean 24-h levels of ACTH, cortisol, and endorphin (11). In addition, daytime cortisol levels during exam increased only in a group of students who perceived that their stress scores increased (11). In our study, we found that students have a higher level of IV and IS during the week of the exam, compared with baseline, which may result from the effect of GC on the SCN due to academic stress. A lower RA results from both decreased daytime activity and increased nocturnal activity.

Sleep responds to a variety of stressors, and ample evidence testifies that the hypothalamic-pituitary-adrenocortical (HPA) axis not only mediates physiological and behavioral responses to stressors but may also be involved in the physiological regulation of waking (7,14). In rats, an immobilization stress of 1 or 2 hours is accompanied by marked polygraphic waking and followed by a significant sleep rebound concerning mainly paradoxical sleep (2). Self-reported sleep problems in Chinese students are common and associated with multiple factors (10). Liu et al (10) reported that life stress experience was significantly associated with an increased risk of insomnia. In the present study, we found that students who suffered from disturbed sleep exhibited lower sleep quality during the week of examination. This was demonstrated by increased wakings, higher total activity scores at night, lower total sleep time and lower sleep quality scores. According to the sleep diary, there is also self-reported wakefulness and there are complaints about sleep quality. This corroborated the results from the actigraph registration.

In conclusion, academic stress did significantly influence the circadian rest-activity and sleep-wake rhythm in healthy female college students, probably due to the effect of corticosteroids on the SCN.

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