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Sodium-Restricted Diet Increases Nighttime Plasma Norepinephrine and Impairs Sleep Patterns in Man*

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ABSTRACT. Plasma norepinephrine levels in 10 healthy young males were significantly elevated after 3 days of a low sodium (<500 mg/day) diet. The low sodium diet was also associated with disturbed sleep patterns: decreased rapid eye movement and slow wave sleep and increased wakefulness. These sleep changes are similar to those seen in normal aged adults, who also undergo elevations of daytime and nighttime plasma norepinephrine. These results suggest the possibility that increased sympathetic nervous system activity may affect sleep patterns, and that therapies altering sympathetic activity may affect sleep. (*J Clin Endocrinol Metab* **56:** 553, 1983)

PLASMA norepinephrine (NE) levels increase with advancing age (1–6). Plasma NE also varies with sympathetic nervous system (SNS) activity, being high during sympathetic activation (2, 4, 7–16) and low during sympathetic inhibition (17, 18). For this reason, plasma NE is considered to indicate the level of SNS activity (10, 11).

Human sleep patterns also undergo changes with advanced age (20–23). Aged individuals tend to sleep less, have less rapid eye movement (REM) and slow wave sleep (SWS), and awaken more during sleep. An earlier study in our laboratory (5) noted a relationship between increased plasma NE and the decreased quality of sleep that occurs with normal human aging. A later study confirmed and expanded these findings (6). NE levels are not increased during spontaneous awakenings from sleep or all night wakefulness (6), suggesting that disturbed sleep *per se* does not induce an elevated plasma NE level. We hypothesize that heightened sympathetic tonus might be interfering with sleep and promoting nighttime wakefulness. To test this, we instituted a dietary restriction of sodium [which results in a mild volume depletion and sympathetic activation (14)] and examined the resulting increase in plasma NE as well as the change in quality of sleep patterns.

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Experimental Subjects

Subjects were paid volunteer young males, aged 23–28 yr (mean, 25.2 yr). They were normotensive nonobese unmedicated nonsmokers and were judged to be in good health on the basis of medical examination, history, electrocardiogram, and pulmonary function tests. Subjects were screened for sleep problems and reported regular sleep habits and no difficulty sleeping. They abstained from alcohol and caffeine for at least 1 week preceding each of the two study periods. They were admitted to the Clinical Research Center, University Hospital, 1 day before each study period and were placed on a standard hospital diet with normal caloric and nutritional content and either normal or restricted sodium content. Subjects spent their time in a controlled ward environment, but maintained their normal sleep habits.

Materials and Methods

After 1 or more nights of habituation, blood samples were drawn, hourly during sleep and more frequently at bed and rise times, for 12 h via an indwelling venous catheter kept patent by a slow saline drip of 1000 IU heparin/100 ml lactated Ringers buffer. Subjects underwent the catheterization procedure 2 h or more before the first blood sampling at 2100 h. Plasma NE was assayed (24, 25) and sleep stages were recorded (26) using techniques previously described (5).

Within 2 months of their first stay in the sleep lab, subjects were recalled, placed on a 3-day sodium-restricted diet (≤500 mg Na), and then restudied in the sleep laboratory as before. All subjects participating in the second half of the study had a mean urinary sodium level less than 50 meq/liter, a concentration associated with elevated plasma NE (14, 27–30). On the day preceding the sleep study, the subjects' mean urinary sodium level was 28.2 ± 4.6 meq/liter.

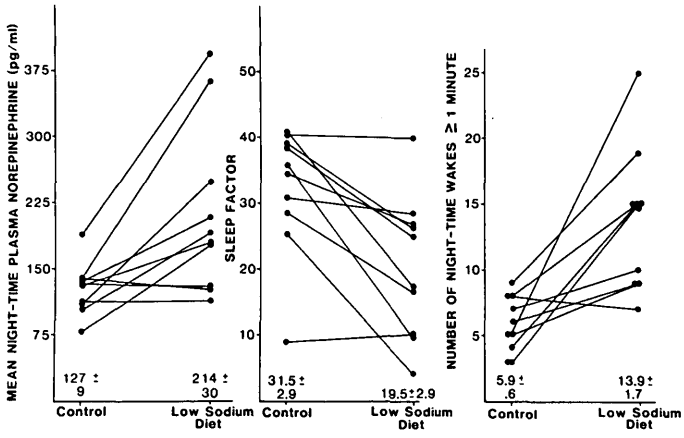

FIG. 1. Mean nighttime plasma NE (picograms per ml), sleep factor, and number of nighttime wakes of 1-min duration or more for each subject in the control and sodium-restricted conditions. The mean and SEM are shown for each variable.

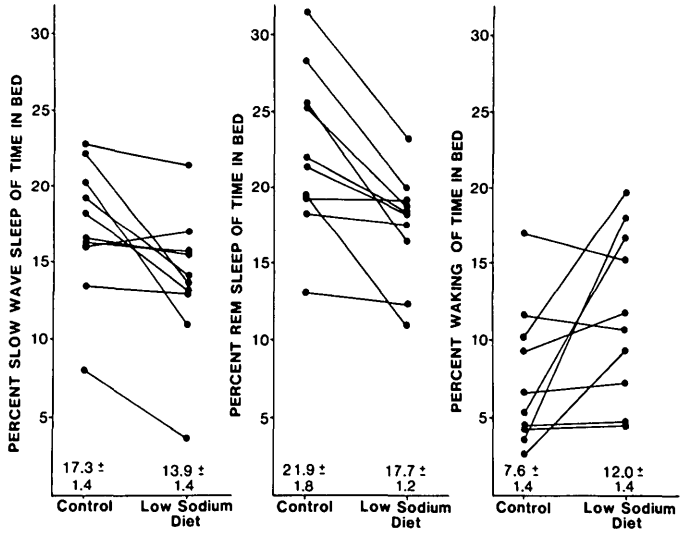

FIG. 2. Percentages of SWS, REM sleep, and waking of total time in bed for each subject under the control and sodium-restricted conditions. The mean and SEM are shown for each variable.

Results

The mean nighttime plasma NE[1] level was significantly elevated after 3 days on the low sodium diet ($P < 0.01$; Fig. 1). Sleep quality was impaired by the diet: sodium-restricted subjects had more total awakenings[2] (22.4 ± 2.6 *vs.* 13.5 ± 1.6; $P < 0.012$), and their number of awakenings of 1 min duration or longer was significantly increased ($P < 0.012$; Fig. 1). The duration of these awakenings was not significantly increased. As shown in Fig. 2, subjects spent less time in SWS ($P < 0.012$) and REM sleep ($P < 0.002$) and more time awake ($P < 0.044$) while on the sodium-restricted diet. Sleep factor,[3] a composite measure of sleep quality, was significantly reduced ($P < 0.004$) after 3 days on the low sodium diet (Fig. 1). Total time asleep was also reduced (407.5 ± 12.2 *vs.* 373.8 ± 14.3 min; $P < 0.043$). Total time in bed, sleep latency,[4] and REM latency[5] were not significantly changed by sodium restriction. The change in the mean nighttime plasma NE level for each subject across conditions was found not to significantly correlate with any of the changes in sleep measures.

Discussion

NE in plasma is believed to be derived mainly from NE released from peripheral postganglionic sympathetic nerve endings, which are particularly numerous in vascular walls (10, 11). Plasma NE is known to be increased in man at times when the SNS is activated by orthostatic challenge (7, 12), exercise (12, 13), mental (8) and cold (9) stress, mild volume depletion (14), myocardial infarction (15), and surgical stress (16) and to be decreased when the SNS is inhibited pharmacologically with clonidine (17) or when sympathetic efferents are blocked with high spinal anesthesia (18). It is reasonable to assume that higher plasma NE levels reflect a heightened sympathetic activation.

It is possible that the observed changes in plasma NE and sleep patterns may be the independent results of dietary sodium restriction; this is supported by the lack of correlation between changes in plasma NE and sleep patterns across control and low sodium conditions. However, there is considerable evidence to suggest an interaction between sleep and the central nervous pathways governing the SNS. Measures of central and peripheral sympathetic activities are known to vary diurnally, with highest levels in the awake part of the diurnal cycle (5). Physiological (31) and anatomical (32) studies indicate that central SNS pathways receiving afferents from baro- and chemoreceptors include dorsal medullary areas. These pathways exert facilitative (33) or inhibitory (34) effects on sympathetic activity levels and contain catecholamine-synthesizing cell bodies (35), as does another major sympathoinhibitory area, the locus ceruleus (36). These brainstem areas have been directly implicated in the control of sleep/wake states (37–39) or have neuroanatomical connections with brainstem areas involved in sleep (40). These pathways also moderate the brainstem reticular system (41), a diffuse pathway which is stimulated by adrenergic inputs and which facilitates the wakeful state (42, 43). Pharmacological studies generally concur that drugs enhancing activity in the central NE

[1] The mean nighttime plasma NE for each subject was the average of all hourly samples from 0.5 h postsleep onset to 0.5 h prerise time.

[2] An awakening is defined by at least 15 sec of α-activity in the electroencephalogram record.

[3] Sleep factor equals the percentage of SWS (stages 3 and 4) of the total time in bed (TIB) plus the percentage of REM of the TIB minus the percentage of time awake of the TIB.

[4] Sleep latency is the time between lights out and sleep onset.

[5] REM latency is the time between sleep onset and REM onset.

synapses predispose toward wakefulness and suppress SWS, while drugs or treatments that decrease activity in central NE synapses predispose toward sleep (44–46). Thus, there is evidence from anatomical, physiological, and pharmacological studies to indicate that the central mechanisms regulating sleep and sympathetic outflow may interact. We hypothesize that this interaction includes a suppression of sleep (along with increased wakefulness) when sympathetic activity is high, as it is during awake hours. The literature on poor sleep in night workers is in accord with this hypothesis (47).

In an earlier study (5) we noted a relationship between the increased plasma NE level and the decreased quality of sleep that occurs with normal human aging; decreased REM and SWS and increased wakefulness. A later study (6) confirmed and expanded these findings; in aged subjects, plasma NE was significantly elevated throughout the 24-h period, with peak concentrations in the late morning and minimal concentrations during bedtime hours for both aged and young groups. Additionally, it was observed that mean nighttime NE levels correlated with sleep/waking measures, indicating poor sleep ($r = -0.694$; $P < 0.001$). Finally, no relationship between plasma NE and either bed- or rise time was observed, nighttime NE levels did not vary according to waking or sleep stage, and no increases in plasma NE were observed during spontaneous wakes, unstressful induced wakes, or night of total sleep deprivation, indicating that disturbed sleep *per se* does not result in elevated plasma NE levels (Prinz, P. N., M. V. Vitiello, and J. B. Halter, in preparation). These observations and the finding of the present study suggest the possibility that high sympathetic tonus (as measured by plasma NE) may underlie some of the fragmentation and deterioration of sleep in the elderly.

The changes of sleep patterns observed in young subjects while sodium restricted are similar to those in aged men who also have elevated NE levels (5, 6) (Prinz, P. N., M. V. Vitiello, and J. B. Halter, in preparation). This suggests that increases in sympathetic nervous activity may impair sleep patterns regardless of whether that increase is the result of aging or of sympathetic stimulation of various kinds. If changes in sympathetic tone do indeed affect sleep patterns, it becomes important to consider the sleep-altering side effects of sympathomimetic and sympatholytic therapies.

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