—**Original**—

Effects of Trazodone and Imipramine on the Biological Rhythm: An Analysis of Sleep EEG and Body Core Temperature

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Abstract

Depression commonly involves abnormalities of the sleep-wake rhythm, the temperature rhythm, and other biological rhythms. The changes of these biological rhythms are caused in remission by medications. However, it has yet to be clarified whether the biological rhythms are changed as a result of recovery from depression or from the direct pharmacological effects of the antidepressants. Therefore, we have undertaken a study on the direct effects of the antidepressants trazodone and imipramine on the biological rhythms of healthy volunteers.

The study involved 12 healthy male volunteers (ages 21~28 years, mean age 23.9 ± 1.7 years) who had given written informed consent. Placebo, trazodone, and imipramine were each administered in a single blind manner four times a day, during the three-day study period. The total daily dosage of trazodone was 100 mg (50 mg in one subject), and of imipramine 40 mg (20 mg in one subject). Subjects were submitted to polysomnography (PSG) and body core temperature (rectal temperature) measurements during the study period. We compared the data concerning the antidepressants to those of the placebo.

The results show that, with regard to the sleep rhythm, trazodone significantly increased slow wave sleep (SWS), but no changes were observed in REM (rapid eye movement) sleep. Imipramine significantly decreased REM sleep and prolonged the REM cycle. With regard to the temperature rhythm, trazodone showed a tendency to advance the appearance time of the minimal temperature. Imipramine significantly lowered the maximal temperature and decreased the difference between the maximal and the minimal temperature, but no changes in the phases were observed. Neither antidepressant had any effect on the temperature cycle.

Trazodone and imipramine showed different effects on PSG. Furthermore, they had different effects on the temperature rhythm. The changes of the sleep-wake rhythm were greater than those of the temperature rhythm. Although the two antidepressants had different mechanisms of action, it is worthy of note that both directly influenced the biological rhythms of healthy volunteers. (J Nippon Med Sch 2002; 69: 333–341)

Key words: trazodone, imipramine, polysomnography, body core temperature, biological rhythm

Introduction

Depressive illnesses are frequently accompanied by abnormalities in the sleep-wake rhythm, the hormone secretion rhythms, and other biological rhythms. Many studies have focused on the biological rhythm to investigate the etiology and pathophysiology of depression. Theories, which concern the biological rhythm, include the phase-advance theory, the desynchronization theory, and the reduced circadian amplitude theory[1–3]. Today, studies have shown that patients with depression do not always show constant changes, such as the phase-advance in the

biological rhythm, but we know that they suffer from some form of rhythm abnormalities. Several symptoms of depression are related to the biological rhythm, such as delay of sleep onset, advance of waking time, and increased intermittent waking; diurnal and seasonal variations in mood changes have also been associated with the biological rhythm.

A neurophysiological approach to examine abnormalities in the sleep-wake rhythm of depressive patients shows distinctive changes on polysomnography (PSG) recordings. Changes in sleep continuity appear in the form of prolonged sleep latency (SL), shortened rapid eye movement latency (REML), shortened sleep period time (SPT), and increased intermittent waking[45]. In the sleep architecture, slow wave sleep (SWS, sum of stage 3 and 4 sleep) is decreased and the sum of stage 1 and 2 (Stage 1＋2) sleep is increased. Changes in the amount of REM (rapid eye movement) sleep still remain in dispute[45]. Overall, however, a general conclusion seems to have been reached, with most studies reporting the advanced REM sleep phase[1,6-8]. We[9] have reported the advanced REM sleep during the daytime in patients with affective disorders on medications in our studies with multiple sleep latency test (MSLT)[10], but others have reported the contrary[3].

While studies on the body core temperature rhythm changes generally agree that during the depressed phase, average temperature rises and temperature amplitude (difference between the maximal temperature and the minimal temperature) decreases, there is still controversy over the appearance time and the phase of the minimal temperature[2,11-14].

Studies on the influences of antidepressants on the sleep-wake rhythm have found that imipramine and many other types of antidepressants suppress REM sleep, with prolonged REML and decreases in the amount of REM sleep, and increase Stage 1＋2 sleep in healthy volunteers[15-18], and similarly in depressed patients[19,20]. The effects of antidepressants on SWS are much less consistent than their effects on REM sleep[21]. Mianserin, trazodone, and other antidepressants with strong 5-HT$_2$ receptor antagonist properties have been shown to increase SWS in healthy volunteers[22-25] as well as in depressed patients and insomnia patients[26,27]. On the other hand, when observing the effects of antidepressants on the body core temperature of depressed patients, most antidepressants, regardless of the type, have been observed to lower the minimal temperature during the night and increase temperature amplitude[3,14]. However, influences on the phases of temperature rhythm have been varied[3,13].

Generally, trazodone and imipramine improve depressive illnesses and change the biological rhythm. However, it has yet to be clarified whether this change is attributable to clinical improvement from depression or to the direct pharmacological effects of the antidepressants on the biological rhythm. Therefore, we have evaluated the direct effects of these two antidepressants on the biological rhythm of healthy volunteers, by monitoring PSG and body core temperature.

Subjects and Methods

(1) Subjects

Twelve healthy paid male volunteers, who gave written informed consent in accordance with the Declaration of Helsinki (modified Hong Kong, 1989) and were aged 21～28 years (mean 23.9±1.7 years), participated in this study. None of the subjects had any history of sleep disorders or any other form of mental disorders, or a history of somatic illness. They all led well-regulated lives and had been completely free of any medication.

(2) Study design (Fig. 1)

The study design was composed of four sessions. The first session was the adaptation session, in which the drug-free subjects were submitted to PSG and body core temperature measurements for three consecutive nights. In the second through the fourth sessions, the subjects were administered each drug. Then they were subjected to PSG for two consecutive nights and body core temperature measurements of more than seventy continuous hours from the day before the first PSG measurement of each session. There was a washout period of at least one week between each session. PSG was measured in the sleep laboratory, where temperature and humidity levels were kept fixed. During the study, all subjects recorded sleep logs and were asked not to sleep during the day. Furthermore, all subjects were instructed to take meals at 8 : 30, 12 : 00, and 18 : 00 and to abstain from caffeine and alcohol throughout the study.
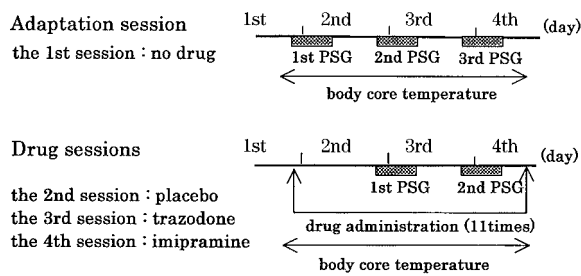
Fig. 1 Study design
This study consisted of four sessions. The first session was the adaptation session without drugs, in which three consecutive PSG and temperature measurements were performed. The second through the fourth sessions were the drug sessions, in which two consecutive PSG and more than 70 hours of temperature measurements were performed. The administration of the drugs, inactive placebo, trazodone, imipramine, took place in this order.

(3) Drug administration

In the drug sessions, all subjects underwent the single-blind administration of inactive placebo, trazodone, and imipramine, in this order. Drug administration took place four times a day, at 8:00, 12:00, 18:00, and 20:00. Total trazodone dosage was 100 mg a day (50 mg in one subject), and total imipramine dosage was 40 mg a day (20 mg in one subject). The first dose was administered at 20:00 of the day preceding the first PSG measurement. A total of eleven doses were administered for three consecutive days, with the last dose administered at 12:00 of the day following the second PSG measurement of each session.

(4) PSG recording

The EEGs were derived from C 3-A 2 and C 4-A1; two electrooculograms (EOG), submental electromyogram (EMG), and electrocardiogram (ECG) monitoring were also carried out. The PSG recordings were taken from 22:00 to 7:00 of the following day. We scored the PSG parameters by visual assessment using the standard criteria[28]. The following data were analyzed as sleep continuity indices: sleep latency (SL, the time span between "lights out" and onset of the first stage 2 sleep); REM latency (REML, the time span between sleep onset and onset of the first REM sleep); sleep period time (SPT, the total time between sleep onset and sleep end); sleep efficiency index (SEI, the percentages of the sleep time for the recording time). The following were analyzed as sleep architecture indices: the percentage of SWS for SPT (%SWS); the total amount of REM sleep over the night (total REM); the percentage of REM sleep for SPT (%REM); the percentage of the sum of stage 1 and 2 sleep for SPT (%Stage 1+2). As REM sleep indices, the following were analyzed:REM cycle, which is defined as the period from the end of a REM episode until the end of the next REM episode, and the number of REM cycles per night (number of REM-cycle); mean duration of REM cycles (MREM-cycle); mean duration of REM sleep for one REM cycle (MREM-period). Two consecutive PSG recordings were performed during each session, but since no significant statistical differences were observed, we used the mean value of the two in our analysis.

(5) Body core temperature (rectal temperature)

Rectal temperature was measured as an index of body core temperature. A temperature logger (Kohden Medical Co.; KMC-604) was used to make consecutive measurements every five minutes. Recordings were obtained for at least seventy consecutive hours, from the administration of the first dose to the end of each session. The temperature probe was inserted at least 10 cm into the anus. Rectal temperature parameters were scored by visual assessment. We measured the following parameters: the maximal temperature (maxTP); the minimal temperature (minTP); the average of maxTP and minTP (meanTP); the difference between maxTP and minTP (difTP). After finding the appearance time of maxTP (Tmax) and the appearance time of minTP (Tmin), the following parameters were calculated: the length from the first Tmax until the second Tmax (period-Tmax); the length from the first Tmin until the second Tmin (period-Tmin); the mean rate of decline from maxTP to minTP (mean-decTP); the maximum rate of decline from maxTP to minTP in one epoch (max-decTP); the appearance time of max-decTP (Tmax-decTP). Two values each (the values from the first and second measurements), except for the period-Tmax and the period-Tmin, were available for each session; since there was no significant difference between the two values, we used the mean of the two values in our analysis.

(6) Statistical analysis

StatView Ver. 5.0 was used in the statistical analysis. We performed one-factor ANOVAs for the sleep parameters and the temperature parameters. We further went on to calculate the Fisher's PLSD (Protected Least Significant Difference) and examined changes by comparing the values of trazodone and imipramine to those of the placebo. We evaluated the p-value as statistically significant when the p-value was below 0.05 and as a tendency when the p-value was between 0.1 and 0.05.

Results

1. PSG parameters

The results of the PSG parameters are shown in **Table 1**. No significant group differences were observed on SL, SPT, or SEI in the one-factor ANO-VAs. We further went on to calculate the Fisher's PLSD when significant between-group differences were observed in the other PSG parameters. Trazodone had an effect on non-REM sleep parameters: a

significant increase in %SWS (p<0.01) and decrease in %Stage 1+2 (p<0.05). However, trazodone did not have any effect on REM sleep parameters: REML, %REM, total REM, number of REM-cycle, MREM-cycle, or MREM-period. Imipramine suppressed REM sleep parameters significantly: it prolonged REML(p<0.01), decreased%REM(p<0.01), total REM (p<0.01), and number of REM-cycle (p<0.01), and significantly increased MREM-cycle(p<0.01). However, no changes were observed in MREM-period. The effects of imipramine on non-REM sleep parameters were varied: %SWS was not affected, while %Stage 1+2 showed significant increase (p<0.01).

2. Temperature parameters

The results of the temperature rhythm are shown in **Fig. 2**, and the more precise changes in the parameters in **Table 2**. No significant group differences were observed on minTP, Tmax, period-Tmax, or period-Tmin in the one-factor ANOVAs. We further went on to calculate Fisher's PLSD when significant (p<0.1) between-group difference

Table 1 Results of PSG parameters (mean ± s.d.; n = 12)

PSG parameters		Placebo	Trazodone[a]	Imipramine[a]	F-value[b]	P-value[b]
SL	(min)	32.64 ± 25.33	34.53 ± 30.90	22.63 ± 22.00	F = 0.71	NS
REML	(min)	103.43 ± 21.53	108.89 ± 36.56	163.71 ± 62.15 ***	F = 7.07	P < 0.01
SPT	(min)	502.25 ± 24.22	502.76 ± 29.53	512.36 ± 21.52	F = 0.60	NS
SEI	(%)	93.73 ± 4.46	93.87 ± 5.34	95.04 ± 4.69	F = 0.27	NS
%SWS	(%)	14.88 ± 4.90	22.29 ± 8.19 ***	10.79 ± 4.35	F = 11.14	P < 0.01
%REM	(%)	20.69 ± 4.78	22.20 ± 3.08	12.56 ± 4.24 ***	F = 19.28	P < 0.01
%Stage 1 + 2	(%)	64.36 ± 8.35	55.97 ± 9.21 **	75.98 ± 6.82 ***	F = 18.07	P < 0.01
total REM	(min)	103.79 ± 23.21	111.04 ± 14.41	64.29 ± 21.18 ***	F = 19.07	P < 0.01
number of REM-cycle	(times)	4.50 ± 0.77	4.21 ± 0.75	3.29 ± 0.69 ***	F = 8.77	P < 0.01
MREM-cycle	(min)	107.71 ± 15.93	113.41 ± 17.30	154.65 ± 32.68 ***	F = 14.57	P < 0.01
MREM-period	(min)	23.69 ± 7.29	27.03 ± 5.07	13.69 ± 4.69	F = 4.82	P < 0.05

[a]Fisher's PLSD; * P < 0.1 vs placebo, ** P < 0.05 vs placebo, *** P < 0.01 vs placebo
[b]main effect of drug (one-factor ANOVA)
SL = sleep latency (SL is defined as the time span between "lights out" and onset of the first stage 2 sleep.)
REML = REM (rapid eye movement) latency (REML is defined as the time span between sleep onset and onset of the first REM sleep.)
SPT = sleep period time; the total time between sleep onset and sleep end
SEI = sleep efficiency index; the percentages of the sleep time for the recording time
%SWS = the percentage of SWS (slow wave sleep) for SPT
%REM = the percentage of REM sleep for SPT
%Stage 1 + 2 = the percentage of the sum of stage 1 and 2 sleep for SPT
total REM = the total amount of REM sleep over the night
REM-cycle is defined as the period from the end of a REM episode until the end of the next REM episode.
MREM-cycle is defined as mean duration of REM cycles.
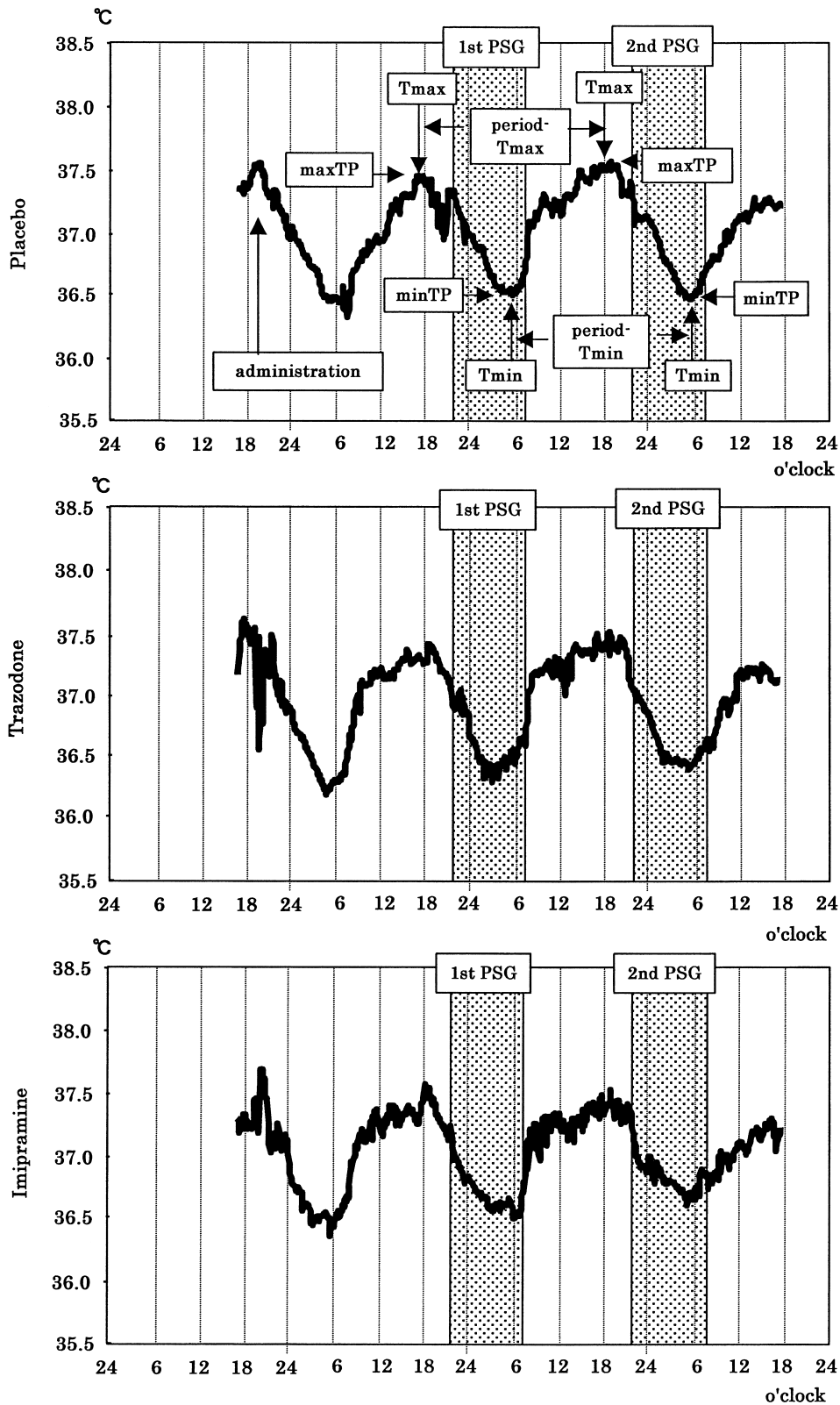MREM-period is defined as mean duration of REM sleep for one REM-cycle.

Fig. 2 Body core temperature

The changes of the average temperature for each drug, inactive placebo, trazodone, imipramine, are shown. The vertical axis is the temperature, and the horizontal axis is the time course. The shaded portion of the figure shows the time during which the PSG was performed. Each temperature parameter is shown here. The upper shows inactive placebo administration, the middle shows trazodone, and the bottom imipramine.

was observed in the other temperature parameters. When the effects of trazodone were compared to those of the placebo, maxTP and meanTP showed tendencies to decrease (p<0.1), while Tmin tended to advance (p<0.1). On the other hand, when the effects of imipramine were compared to those of the placebo, it significantly lowered maxTP and difTP (p<0.05), but no changes were observed with respect to Tmax or Tmin. Neither antidepressant had any effect on the temperature cycle—the period-Tmax or the period-Tmin. Imipramine decreased the max-decTP significantly (p<0.01), and tended to delay the Tmax-decTP (p<0.1). However, trazodone did not show any effect on the parameters related to the temperature decline.

Discussion

Imipramine is a typical tricyclic antidepressant which acts as both a noradrenaline and serotonin reuptake inhibitor, although its function as the former is more pronounced[29].Trazodone is categorized pharmacologically as a selective serotonin reuptake inhibitor[29] and a 5-HT 2 blocker[21]. It has been widely used for treating patients suffering from depressive illness and sleep disorders, for its weak anticholinergic action and cardiac toxicity.

We conducted this study in a single-blind manner; therefore we cannot evaluate how the order of drug administration affected the results.

In this study, although the period of administration was comparatively short, both trazodone and imipramine were administered four times a day, not in a single dose administration at night. Therefore, we believe that each level of blood concentration was maintained steadily throughout the day, affecting the biological rhythm all day. In PSG studies, trazodone, however, has been reported to increase SWS in both healthy volunteers and depressed patients[23,26,27], and its effect on REM sleep has been disputed[25-27,30]. In our study, trazodone increased SWS and showed no changes in the REM sleep. Administration of m-chlorophenylpiperazine (m-CPP), an active metabolite of trazodone, was shown to affect the 5-HT$_1$ receptor, leading to a decrease in SWS[31].Therefore, it can be concluded that an increase in SWS is attributable to the direct pharmacological effect of trazodone. In healthy subjects, the selective serotonin

reuptake inhibitor (SSRI) does not have any effect on the SWS[16,17,21]. Kupfer et al.[20] reported that fluvoxamine showed no changes on SWS in depressed patients. On the other hand, the 5-HT$_2$ receptor antagonists, ritanserin and mianserin, have also been reported to increase SWS[21,22,32,33]. From these facts, we considered that increased SWS from trazodone administration was mediated by the antagonistic actions of the 5-HT$_2$ receptors.

Imipramine mainly worked to suppress REM sleep. Although imipramine significantly suppressed REM sleep in our results, it didn't show any statistical effects on SWS. These results, overall, were in agreement with previous reports[15,18-20]. The total amount of REM sleep decreased, REML became longer, the number of REM-cycle decreased, and MREM-cycle was prolonged. These facts led to the conclusion that imipramine delayed REM sleep phase in the sleep-wake rhythm[34].

Although the effects of trazodone and imipramine on PSG differed in terms of their influences on SWS and REM sleep, they both showed influences in normalizing the sleep EEG of depressed patients. The relationship between the antidepressants' effects and REM sleep suppression and increased SWS has been reported in some studies[19,35], and this coincides with the findings of this study. It may be added here that the results of this study have shown that both antidepressants had no influence on sleep continuity parameters—SL, SPT, or SEI. This result may be attributed to the fact that the study involved healthy volunteers who have no sleep disorders and that PSG measurements were performed within a limited schedule. For these reasons, we cannot make any firm conclusion on the effects of the two antidepressants on sleep continuity from this study.

There have been many studies reporting on the relationship between sleep and body temperature. The heat-releasing mechanism has been reported as a function of SWS[36]. Berger et al.[37] reported that increased SWS leads to greater release of body heat, which in turn leads to minimal temperature decline. Adversely, looking at the effect of body temperature on sleep shows that the sharp drop in body temperature from evening on into the night induces sleep, bringing on sleep onset and increasing SWS[36,38].Rise in body temperature from the minimal temperature leads to awakening. On the other hand, there have

Table 2   Results of temperature parameters(mean ± s.d.; n = 12)

(visual assessment of actual measurements)

temperature parameters		Placebo	Trazodone[a]	Imipramine[a]	F-value[b]	P-value[b]
maxTP	(℃)	37.81 ± 0.14	37.68 ± 0.15 *	37.67 ± 0.21 **	F = 2.78	P < 0.1
minTP	(℃)	36.38 ± 0.23	36.23 ± 0.27	36.44 ± 0.33	F = 1.83	NS
meanTP	(℃)	37.10 ± 0.17	36.95 ± 0.19 *	37.06 ± 0.22	F = 1.71	P < 0.1
difTP	(℃)	1.44 ± 0.17	1.45 ± 0.21	1.23 ± 0.32 **	F = 3.03	p < 0.1
Tmax	(time)	17.20 ± 1.97	17.31 ± 2.32	18.01 ± 1.19	F = 0.65	NS
Tmin	(time)	6.11 ± 1.40	5.13 ± 1.56 *	6.22 ± 1.04	F = 2.39	P < 0.1
period-Tmax	(hr)	23.491 ± 3.408	24.585 ± 1.804	24.475 ± 1.882	F = 0.71	NS
period-Tmin	(hr)	24.107 ± 1.456	24.067 ± 2.184	24.621 ± 1.778	F = 0.34	NS
mean-decTP	(℃/hr)	− 0.12 ± 0.03	− 0.13 ± 0.03	− 0.10 ± 0.03	F = 3.29	P < 0.05
max-decTP	(℃/5min)	− 0.02 ± 0.02	− 0.02 ± 0.01	− 0.05 ± 0.02 ***	F = 11.95	P < 0.01
Tmax-decTP	(time)	17.36 ± 2.43	18.79 ± 1.99	18.82 ± 1.74 *	F = 1.95	p < 0.1

[a]Fisher's PLSD; * P < 0.1 vs placebo, ** P < 0.05 vs placebo, *** P < 0.01 vs placebo

[b]main effect of drug(one-factor ANOVA)

maxTP = the maximal temperature

minTP = the minimal temperature

meanTP = the average of maxTP and minTP

difTP = the difference between maxTP and minTP

Tmax = the appearance time of maxTP

Tmin = the appearance time of minTP

period-Tmax = the length from the first Tmax until the second Tmax

period-Tmin = the length from the first Tmin until the second Tmin

mean-decTP = the mean rate of decline from maxTP to minTP

max-decTP = the maximum rate of decline from maxTP to minTP in one epoch

Tmax-decTP = the appearance time of max-decTP

been reports that there is no direct relationship between SWS and body temperature[39,40], while others have reported a correlation with REM sleep[7,41].

From the results of the body temperature parameters, we found that although trazodone increased SWS, meanTP and maxTP showed only insignificant decline, and there was no change in minTP. The fact that it increased SWS without lowering minTP is of great interest. Imipramine, on the other hand, was observed to have lowered maxTP and decreased difTP significantly. This meant that imipramine decreased the amplitude of the temperature rhythm. Although this finding is in conflict with previous reports[3,13,14], we may conclude that imipramine has a direct pharmacological effect on the temperature rhythm.

With regard to the relationship between body temperature decline and sleep, neither antidepressant caused any significant change in the mean-decTP. However, the results with imipramine showed a significant change in the max-decTP, and a tendency for delay of the Tmax-decTP. Murphy et

al.[38] have reported the relationship between the increased maximal decline of temperature and the shortened SL and the increased SWS in temporal isolation studies with healthy volunteers. In our experiment, there was no change in SL from the two antidepressants, and there was no change in SWS from imipramine administration. From these results, we cannot obtain a clear relationship between the maximal decline of temperature and SWS.

With regard to the phases of the temperature rhythm, although trazodone did not affect Tmax, Tmin showed a tendency to advance by one hour. However, we cannot conclude that trazodone influenced the phases of the temperature rhythm, because this change was not statistically significant, although we can suggest this possibility. We cannot, however, reach a conclusion on the relationship between advance of Tmin and the waking time, as almost all subjects woke up at 7:00, the termination time of the measurements. Imipramine had no effect on the phases of the temperature rhythm: it caused no changes in Tmax or Tmin. Wever[42] has reached

the assumption, from the temporal isolation studies conducted, that there are two different autonomic oscillators, one controlling the temperature rhythm, and another controlling the sleep-wake rhythm. The former was thought to have a stronger influence on the circadian rhythm. Together with the fact that the subjects of this study were healthy volunteers whose homeostasis was normal, the dosage and duration of drug administration may not have been enough for the antidepressants to exert any influence on the phases of the temperature rhythm. However, in view of the fact that imipramine affected the amplitude of the temperature rhythm, as well as suppressing REM sleep, a relationship between REM sleep and the temperature rhythm may be suggested. On the other hand, we can suggest some relationship between SWS and the temperature rhythm due to the increase in SWS and the changes in some temperature parameters under trazodone administration. Body temperature may have been altered due to the strong masking effects of daily activities, such as eating. It was difficult to keep these factors under control when the subjects continued with their daily lives while participating in the experiment. We will need to further examine the effects of these factors on our results.

In this study, we examined the effects of trazodone and imipramine on the sleep-wake rhythm and the temperature rhythm of healthy subjects. As a result, trazodone showed an increase in the amount of SWS on PSG and the tendency for advanced appearance time of the minimal temperature. Imipramine showed suppression of REM sleep on PSG, and a decrease in the amplitude of temperature and a decline of the maximal temperature. Although the two antidepressants differed in their effects, both had direct pharmacological effects on the biological rhythms of the healthy subjects. We suggest that these different effects are based on the pharmacological actions of each antidepressant, mainly trazodone acting on the 5-HT$_2$ receptors, and imipramine mainly acting on the noradrenaline receptors. Although we recognized the direct effects of the sleep-wake rhythm on the normalizing of the abnormal sleep-wake rhythm in depressed patients, we made no similar observations concerning temperature rhythm. It should be noted that both antidepressants had effects on the biological rhythms of healthy

subjects. But there was a great discrepancy between the sleep-wake rhythm and the temperature rhythm induced by each antidepressant, i. e. the changes of the sleep-wake rhythm were greater than those of the temperature rhythm. The results of this study lead us to conclude that we have to further clarify the direct effects on the biological rhythms of both antidepressants by reconsidering adequate dosage and duration of drug administration in a future study.

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