—Original—

Double Blind Study of Melatonin Effects on the Sleep-wake Rhythm, Cognitive and Non-cognitive Functions in Alzheimer Type Dementia

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Abstract

Previously, we reported that morning bright light therapy improved sleep time and cognitive function in Alzheimer type of dementia. We conducted a double blind study to examine the effects of melatonin on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type of dementia. The subjects were 9 persons given a placebo (PLA), and 11 given melatonin (3 mg) (MLT). The mean age was 79.2±6.4 (17 females and 3 males). The drugs were given at 20: 30 each day for 4 weeks. We checked sleep time and activity by Actigraph through one week before and the 4 th week after drug administration. Cognitive and non-cognitive functions were evaluated with the clinical dementia rating scale (CDR), and Mini Mental State Examination (MMSE), and the Alzheimer's Disease Assessment Scale (ADAS). We successfully recorded Actigraph data from 18 patients (PLA 8, MLT 10). The mean sleep time change ratio and SD of the administration of PLA in the night was −0.2±13.7 %, and MLT was 33.2±37.6%. The mean activity counts and SD of the administration of PLA in the night was 29.8±77.0%; in MLT it was −44.9±21.9%. Melatonin significantly prolonged the sleep time ($p=0.017$) and decreased activity ($p=0.014$) in the night (21: 00〜6: 00) in the MLT group, although no significant difference in sleep time or activity in the daytime (6: 00〜21: 00) was recognized between the two groups. In comparison with ADAS cognition score changes, the mean change and SD in the PLA was 0.3±3.7; in MLT it was −4.3±3.6 points. In comparison with ADAS non-cognition score, the mean change and SD in the PLA group was −0.8±1.0, in the MLT group it was −4.1±2.2 points. There were also significant differences between the PLA and the MLT groups in the comparison with the score improvement of ADAS cognition ($p=0.017$) and non-cognition ($p=0.002$), otherwise there was no significant difference in improvement of MMSE between both groups.

Melatonin administration had effect to improve sleep time and night activity, but no significant effect to improve daytime naps and activity. Although melatonin administration might has less strong effect on circadian rhythm than morning bright light therapy we previously reported, cognitive and non-cognitive functions were improved. Melatonin seemed to be useful for care of the Alzheimer type of dementia patients.
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Key words: Melatonin, Alzheimer type dementia, sleep-wake rhythm, cognitive function, non-cognitive function

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Introduction

The disturbances of sleep-wake rhythm, disturbance of behavior and delirium in the night are often observed in Alzheimer type dementia (ATD) patients. And hypersomnia and conscious disturbance like sleepiness are also sometimes recognized in the daytime. Previously, co-author Ito et al. reported that bright light therapy improved the disturbance of sleep-wake rhythm, behavior in night, cognitive and non-cognitive functions in the daytime on ATD[1]. It is known that melatonin is one of hormone secreted from pituitary gland and indicator of function of suprachiasmatic nucleus (SCN). SCN plays a main role of circadian rhythm regulation and the number of nerve cells of SCN decreases by aging[2,3].

Rod et al.[4] reported that small dosage of melatonin advances or delayed the phase of sleep-wake rhythm and large dosage of melatonin has a hypnotic effect. Brusco et al.[5,6] also reported that melatonin improved the sleep disturbance patients in open study. Therefore, melatonin seemed to have efficacy for the improvement of sleep-wake rhythm disturbance of ATD. We suspected that the melatonin rise the vigilance in the daytime due to the improvement of sleep disturbance.

We conducted this study to evaluate melatonin effects on the disturbance of sleep-wake rhythm in the night and daytime, cognitive and non-cognitive function with a double blind control method.

Method

Subjects

All subjects were the admitted patients in the geriatric ward of S Hospital during 2000～2002. Patients were diagnosed as Alzheimer type dementia with brain CT or brain MRI and EEG for physical examination, and Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the Clinical Diagnosis of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) for diagnostic criteria[7]. Those patients had no severe physical diseases and had no disorders cause sleep disorders besides ATD. When patients have been given psychotropics, beta-blockers, which suppresse melatonin secretion[8] or drugs that affect on sleep-wake cycle, we washed out those drugs for 4 weeks before start the study. The drugs that cannot stop taking and cannot affect Alzheimer type dementia were kept given the same dosages throughout the study. Before enrolling in the study, all subjects and protectors were given a full explanation of the purpose of the study and all gave written informed consent to participate (certification from the Research Ethics Committee of S Hospital).

Table 1 Schedule

	1 week	3 weeks	1 week
adaptation	pre-medication	medication	
reduce and stop psycotropics or another drugs effect on patients' sleep wake cycle and cognition	actigraph CDR MMSE ADAS	observation	actigraph CDR MMSE ADAS

Procedures

1. Drugs

Two drugs were used in this study, melatonin 3 mg (MLT) and placebo (PLA), and patients were given the drug at 20: 30. The drugs were administrated in a double blind design by randomized allocation.

2. Study condition

Patients were given meals at 8: 00, 12: 00, 18: 00 and lights were off at 21: 00, and given a bath twice a week at 11: 00. Patients were allowed to spend a time freely in geriatric ward besides mentioned above. We paid attention to avoid any factor to influence their daily life.

3. Study schedule (**Table 1**)

This study composed of 3 blocks.

(1) Adaptation block

Patients were spent time under hospital schedule by mentioned above at 1st week.

(2) Pre-medication block

Patients were evaluated the severity by clinical dementia rating scale (CDR), the cognitive functions by Mini Mental State Examination (MMSE), the cognitive and non-cognitive function by Alzheimer's Disease Assessment Scale (ADAS) and the circadian rhythm by Actigraph through 1 week without medication.

(3) Treatment block

Drugs were given for 4 weeks. The evaluation of CDR, MMSE, ADAS, and Actigraph were checked at 4 th week.

4. Materials

(1) Actigraph

We used portable, wristwatch type Actigraph (Mini Motionlogger Actigraph, Ambulatory Monitoring Inc. U.S.A.) to check the patient's moving. We recorded Actigraph with Zero Crossing mode (ZCM), one epoch 60 seconds and amplitude 18 with non-dominant hand. Actigraph is sensitive to accelerations of 0.1 G (1 activity counts). Actigraph data were measured continuously through one week. We choose serial three days in which there were relatively less artifacts such as non-responded moments due to patients' wearing off the Actigraph logger, and we calculate the average counts of every minute through 24 hr. Activity counts (the number of movements) are accumulated in every minute. We analyzed the records using Cole's algorithm, which judges whether the patient is sleeping or not every one minute[9] and calculated sleep time and activity counts of the night (21: 00～6: 00). And also we calculated same data in the daytime (6: 00～21: 00).

(2) CDR, MMSE. ADAS

1) CDR:

We evaluated the grade of severity by using CDR. CDR is a clinical scale for the staging of demented patients. It determines grade of severity of there behavioral and cognitive dysfunction by 5 stage (0, 0.5, 1, 2, 3)[10]. 3 points is the most severe stage.

2) MMSE:

MMSE is developed as a scale to check the cognitive state simply of demented in patients, especially in epidemiological research. High scores indicate good cognitive state; below 20 (full mark is 30 points) points do dementia, delirium[11].

3) ADAS:

ADAS is composed of 2 detailed scales.[12] Former (as ADAS cognition (ADAS cog.)) is composed of 1) spoken language ability, 2) comprehension of spoken language, 3) recall of test instructions, 4) word-finding difficulty, 5) following commands, 6) naming, 7) objects, fingers, 8) constructions, 9) ideational praxis, 10) orientation, 11) word recall and word recognition.

Later (as ADAS non-cognition (ADAS non-cog.)) is composed of 1) tearful, 2) appears/reports depressive mood, 3) concentration, 4) distractibility, 5) uncooperative to testing, 6) delusions, 7) hallucinations, 8) pacing, 9) increased motor activity, 10) tremors and increase/decrease appetite.

High scores indicate severe disturbance. ADAS has no study effects; therefore we can use it repeatedly to evaluate the change of cognitive state. ADAS cognition is fully marked at 70 points as the worst, and as the cognitive function getting better, the points decreasing. ADAS non-cognition is fully marked at 50 points as the worst, and the points decreasing as same.

5. Statistical method

We used unpaired t-test at evaluation of change ratio of sleep time and activity counts between pre and post (4 th week after administration), Mann Whitney U-test at evaluation of cognitive and non-cognitive functions, on PLA versus MLT administration effects (Double difference[13]). The results were given as mean ± SD.

Results

1. Patient's background (**Table 2**)

We studied 20 patients (PLA 9, MLT 11). We could finally measure sleep time and activity counts by Actigraph on 18 patients (PLA 8, MLT 10). The reason of unsuccessful measurement of Actigraph was patients' resistance to wear watchtype Actigraph on their arm through the week under measurement.

2. The effect on sleep-wake cycle measured by Actigraph:

Table 3 shows raw data of sleep time and activity counts pre and post administration of PLA and

MLT.

(1) The effects on the night (21: 00～6: 00)

1) **Fig. 1** shows the change ratio of the mean sleep time of PLA and MLT in the night, which were obtained from the difference between pre and post (post-pre/pre (%)). The mean sleep time change ratio and SD of administration of PLA was－0.2±13.7%. The mean and SD of administration of MLT was 33.2±37.6%. In patients, there was a statistical significant difference ($p=0.017$) of sleep time change ratio between both groups in the night by unpaired t-test.

2) **Fig. 2** shows the change ratio of the mean activity counts of PLA and MLT in the night, which was obtained from the difference between pre and post (post-pre/pre (%)). The mean activity counts and SD of administration of PLA was 29.8±77.0%. The mean and SD of MLT was－44.9±21.9%. In patients, there was a statistical significant difference ($p=0.014$) of activity counts in the night by unpaired t-test.

(2) The effects on the daytime (6: 00～21: 00)

1) **Fig. 3** shows the change ratio of the mean sleep time of PLA and MLT in the daytime, which was obtained from the difference between pre and post (post-pre/pre (%)). The mean sleep time change ratio and SD of administration of PLA was－26.8±10.2%. The mean and SD of administration of MLT was－5.6±47.8%. In patients, there was no statistical significant difference ($p=0.262$) of sleep time between both groups in the day by unpaired t-test.

2) **Fig. 4** shows the change ratio of the mean activity counts of PLA and MLT in the daytime, which was obtained from the difference between pre and post (post-pre/pre (%)). The mean activity counts change ratio and SD of administration of PLA was 7.0±10.3%. The mean and SD of MLT was 1.5±18.2%. In patients, there was no statistical significant difference ($p=0.486$) of activity counts in the day by unpaired t-test.

3. The effect on cognitive and non-cognitive function:

(1) There was no change in the stage of CDR at every patient.

(2) **Table 4** shows the raw data of MMSE and ADAS cognition and non-cognition scores at pre and post drug administrations.

1) **Fig. 5** shows the mean change of MMSE scores in each group. The mean change and SD of PLA was 1.8±3.2. The mean and SD of MLT was 2.6±1.7 points. There was no statistical significant difference between the PLA group and the MLT group by Mann Whitney's U test ($P=0.210$).

2) **Fig. 6** shows the mean change ADAS cognition scores of each group (ADAS scores shows lower as better). The mean change and SD of PLA was 0.3±3.7. The mean change and SD of MLT was－4.3±3.6

Table 2 Patients' background

mean age 79.2 ± 6.4
case; 20 (male; 3 female; 17)
Lowest 67y.o. Highest 90y.o.
Placebo; 9 mean age 79.4 ± 5.3 (mele; 2 female; 7)
Melatonin; 11 mean age 78.9 ± 7.3 (male; 1 female; 10)
failed measuring actigraph 2 (MLT1 PLA1)

Table 3 Actigraph Data

	21: 00 ～ 6: 00	6: 00 ～ 21: 00
	mean sleep time (minutes), mean±SD	mean sleep time (minutes), mean±SD
PLA pre	383.6±30.1	195.6±65.4
PLA post	383±58.7	145.0±61.6
MLT pre	324.5±64.1	140.4±78.5
MLT post	427.1±29.3	123.5±822.2
	mean activity counts per minutes, mean±SD	mean activity counts per minutes, mean±SD
PLA pre	45.1±21.9	127.8±43.9
PLA post	48.5±27.0	134.0±42.7
MLT pre	67.5±22.1	156.5±45.3
MLT post	33.5±8.1	154.1±37.3

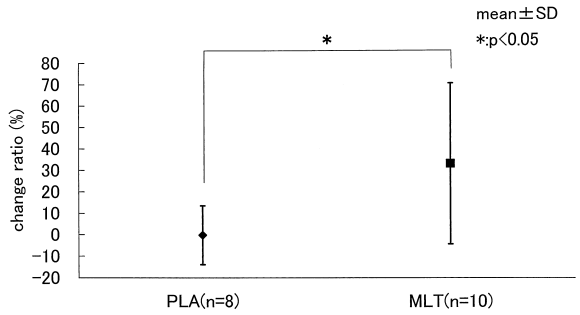

Fig. 1 Shows the change ratio of the mean sleep time of PLA and MLT in the night (21: 00～06: 00). The change ratio was obtained from data (post-pre/pre (%)) of each case. The mean±SD of administration of PLA was −0.2±13.7%, of MLT was 33.2±37.6%. There was a statistical significant difference ($p=0.017$) of sleep time change ratio between both groups in the night by unpaired t-test.

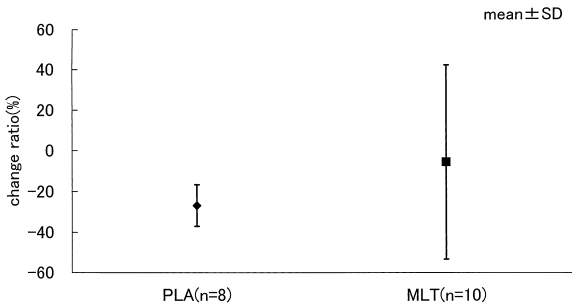

Fig. 3 Shows the change ratio of the mean sleep time of PLA and MLT in the daytime (06: 00～21: 00). The change ratio was obtained from data (post-pre/pre (%)) of each case. The mean±SD of administration of PLA was −26.8±10.2%, of MLT was −5.6±47.8%. There was no statistical significant difference ($p=0.262$) of sleep time between both groups in the day by unpaired t-test.

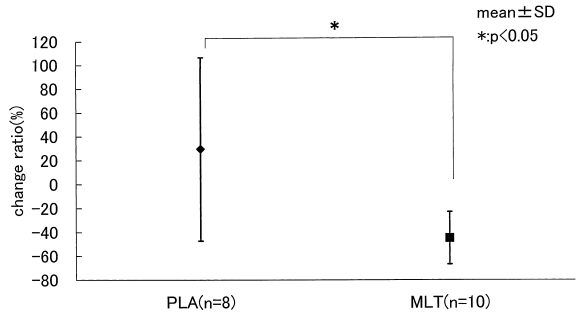

Fig. 2 Shows the change ratio of the mean activity counts of PLA and MLT in the night (21: 00～06: 00). The change ratio was obtained from data (post-pre/pre (%)) of each case. The mean±SD of administration of PLA was 29.8±77.0%, of MLT was −44.9±21.9%. There was a statistical significant difference ($p=0.014$) of activity counts between both groups in the night by unpaired t-test.

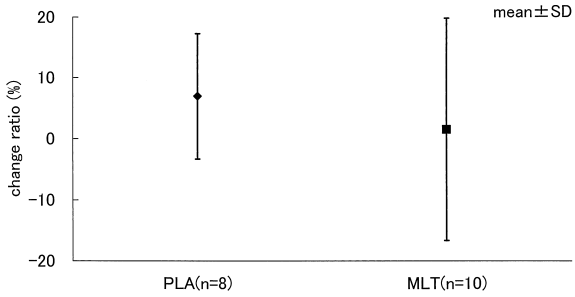

Fig. 4 Shows the change ratio of the mean activity counts of PLA and MLT in the daytime (06: 00～21: 00). The change ratio was obtained from data (post-pre/pre (%)) of each case. The mean±SD of administration of PLA was 7.0±10.3%, of MLT was 1.5±18.2%. There was no statistical significant difference ($p=0.486$) of activity counts in the day by unpaired t-test.

Table 4 MMSE, ADAS scores

	mean MMSE score, mean±SD	ADAS cog. score, mean±SD	ADAS non-cog. Score, mean±SD
PLA pre	10.3±7.5	39.7±17.1	7.9±5.5
PLA post	11.9±8.0	40.0±18.0	7.1±1.1
MLT pre	12.6±7.0	39.8±35.6	10.6±6.0
MLT post	15.3±7.4	35.5±19.5	6.3±4.2

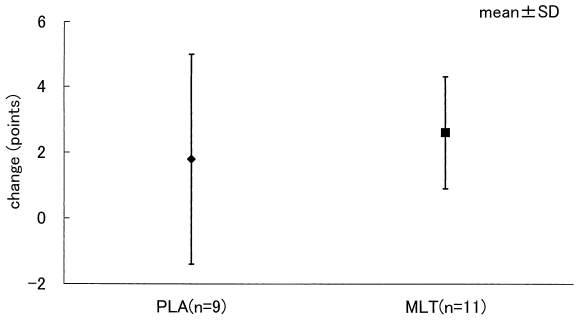

Fig. 5 Shows mean change of MMSE score in each group. The change of score was obtained from difference (post-pre) of each case. The mean±SD of PLA was 1.8±3.2, of MLT was 2.6±1.7 points. There was no statistical significant difference between both groups by Mann Whitney's U test (P=0.210).

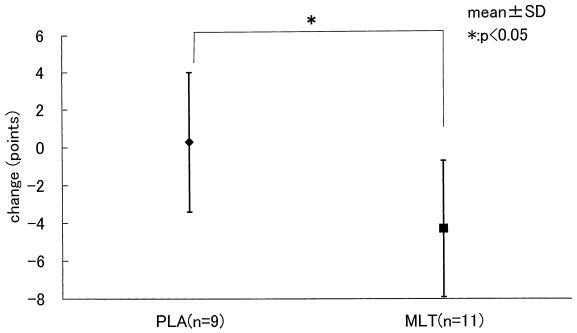

Fig. 6 Shows mean change ADAS cognition scores of each group (ADAS score shows lower as better). The change of score was obtained from difference (post-pre) of each case. The mean±SD of PLA was 0.3±3.7, of MLT was −4.3±3.6 points. There was a statistical significant difference between both groups by Mann Whitney's U test (p=0.017).

points. There was a statistical significant difference between the PLA group and the MLT group by Mann Whitney's U test (p=0.017).

3) **Fig. 7** shows mean change ADAS non-cognition scores of each group (ADAS scores shows lower as better). The mean change and SD of PLA group was −0.8±1.0. The mean and SD of change of MLT group was −4.1±2.2 points. There was a statistical significant difference between PLA group and MLT group by Mann Whitney's U test (p=0.002).

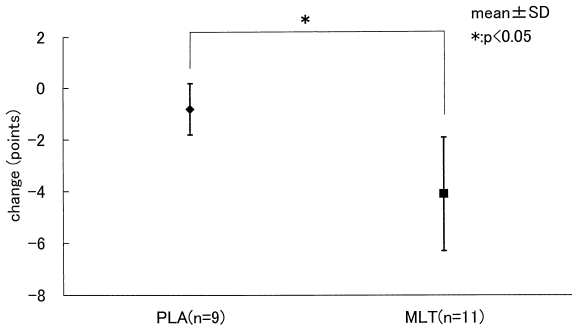

Fig. 7 Shows mean change ADAS non-cognition score of each group (ADAS score shows lower as better). The change of score was obtained from difference (post-pre) of each case. The mean±SD of PLA was −0.8±1.0; of MLT was a −4.1±2.2 points. There was a statistical significant difference between both groups by Mann Whitney's U test (p=0.002).

Discussion

In the biosynthesis of MLT (N-acetyl-5-methoxytryptamine), tryptophan is first converted by tryptophan hydroxylase to 5-hydroxytryptophan, which is decarboxylated to serotonin. The synthesis of MLT from serotonin is catalyzed by two enzymes (arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase) that are largely confined to pineal gland[14,15]. Photic information from the retina is transmitted to the pineal gland through the suprachiasmatic nucleus of the hypothalamus and the sympathetic nervous system. The neural input to the gland is norepinephrine, and the output is MLT. The synthesis and release of MLT are stimulated by darkness and inhibited by light. With the onset of darkness, the photoreceptors release norepinephrine, thereby activating the system, and the number of α 1 and β 1-adrenergic receptors in the gland increase[16]. When the activity of arylalkylaminic N-acctyltransferse, the enzyme that regulates the rate of MLT synthesis, is increased, it initiates the synthesis and release of MLT. The daytime rhythm in serum MLT concentrations parallels the day—night cycle[17,18]. The circadian rhythm of MLT secretion is of endogenous origin, this reflects signals originating in the

suprachiasmatic nucleus[19].

As already mentioned in the introduction, a small dosage of MLT advances or delayed the phase of sleep-wake rhythm and a large dosage of MLT has a hypnotic effect on geriatric subjects suffering from insomnia[4].

Recently, Swaab et al.[2,20] reported that the cell numbers of suprachiasmatic nuclei decrease with aging. Other studies on ATD patients compared age matched controls; they showed lower MLT levels than in normal controls[21,22]. Mishima et al.[23] reported a higher degree of irregularities of MLT secretion is related to age and severity of impaired mental function. ATD decreases slow wave sleep and rapid eye movement (REM) sleep. This induces an increase in sleep fragmentation including daytime naps[24]. Also circadian rhythm disorders in ATD and sleep-wake rhythm or behavioral disturbances are closely correlated[25,26]. Therefore, the lowering of sleep quality itself can be the one factor of mental dysfunction and, also it can induce desynchronization of circadian rhythm causing a lowering of sleep quality and mental function.

Our previous study showed the bright light therapy effected the improvement of the MMSE and ADAS scores and results in an increase in night sleep and decrease in daytime naps in ATD patients. Successful attempts to treat sleep-wake and behavioral disturbances with bright light therapy were also reported[27,28]. So we expected melatonin have a similar effect to bright light therapy in ATD patients.

In this study, we used 3 mg MLT. The dosage is rather higher, therefore MLT seemed to have a hypnotic effect on patients. In fact, MLT improved sleep time and activity in the night, and also cognitive and non-cognitive functions. Recently, Haffmans et al[29] reported that they could not recognize the additional effects of MLT on the bright light therapy effect. They explained melatonin might cause the overshoot for the chronobiological synchronization or the timing of intake.

Improvement in an ADAS score in MLT administration is not considered a direct effect of MLT in this study. We had already reported that bright light therapy improved cognitive function and sleep-wake rhythms on ATD patients. In that study we considered that the improvement of sleep quality secondarily improved the cognitive function and behavioral problems in ATD patients. MLT has a hypnotic effect; this hypnotic effect might secondarily cause the improvement of daytime cognitive and non-cognitive functions in this study. Previous studies reported that bright light therapy has effects on ATD patients, advancing the circadian rhythm (core body temperature rhythm, melatonin secretion rhythm). Morning bright light seemed to affect night sleep and daytime activity by changing the circadian rhythm. In this study MLT administration did not affect daytime activity. This might be explained that the influence to circadian rhythm of MLT is less strong than morning bright light therapy. At this point, more precise study is needed.

In general, benzodiazepines have been used as a hypnotics, but these drugs have side effects: REM suppression in the sleep structure, muscle reluctance and carry-over effects. These drugs sometimes cause delirium in the night, stumbling and sleepiness in the daytime, especially in aged people. MLT is thought to be useful in ATD to improve sleep-wake rhythm without any side effects. This point is very important for caregivers to recognize in patients suffering from abnormal behaviors, for example, wondering, violation of other patients or caregivers, etc. Administration of melatonin also has useful effect in decreasing the burden of caregivers.

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