S-2-6 Sleep-Wake Rhythm Disorders and Vitamin B₁₂

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I. INTRODUCTION

Recent progress in chronobiology has prompted investigators to recognize the disorders which seem to be caused by dysfunction of the circadian clock system. A typical rhythm disorder is the sleep-wake cycle disorder. They are divided into the following three major subtypes.

1. Non-24 hour sleep-wake syndrome

This syndrome is characterized by a chronic steady pattern with 1-2 hour daily delays in sleep and wake times. In normal individuals sleep onset and wake times occur at a period about every 25 hours when they are isolated from environmental time cues. In patients with this syndrome the same pattern is observed in spite of living in society.

2. Delayed sleep phase syndrome (DSPS)

In patients with this syndrome the major sleep episode is delayed in relation to the desired clock time. The patients suffer from a severe difficulty in falling asleep at night. Once sleep has begun they are able to maintain sleep, so they often fail to awake at the desired time during the day. They are unable to advance the sleep phase to earlier hours by enforcing a conventional sleep phase.

3. Irregular sleep-wake cycle

This pattern consists of temporarily disorganized and variable sleep and waking behavior. No regular pattern of the sleep-wake cycle is observed for a long period. Sometimes patients do not sleep at all through a day, while they sleep more than 12 hours on the next day.

Recently several investigators reported a successful treatment of the non-24 h sleep-wake syndrome with vitamin B₁₂ [1,2]. In our recent preliminary study vitamin B₁₂ also seemed to benefit both the non-24 h sleep wake syndrome and DSPS. However, since the sleep-wake cycle is markedly affected by psycho-social factors, we have to be very cautious as to our final conclusion. So, we have organized a multicenter study to establish the effect of vitamin B₁₂ on rhythm disorders.

Here we introduce 3 patients with various rhythm disorders who were benefited by methylcobalamin and report the results obtained by our multi-center study. Moreover, we discuss the underlying mechanism on the usefulness of vitamin B₁₂ with the aid of the results obtained from animal experiments.

II. CASE REPORTS

1. Case 1: A 22-year-old female college student (Non-24 hour sleep wake syndrome):

She manifested a psychotic reaction one year after she entered college in the USA when she was 19 years old. Owing to a conflict with classmates, she became very sensitive and suspicious, and had persecutory delusion. The symptoms were ameliorated by antipsychotic drugs administered after she returned to Japan, but thereafter she suffered from postpsychotic depression. Although the depressive state disappeared 9-10 months later, she suffered from a non-24 h sleep-wake syndrome for 2 months which occurred about 6 months after she recovered from her depressive state. Her rhythm disorder was successfully treated with methylcobalamin at a dose rate of 1.5mg per day (Fig 1-a).

2. Case 2: A 27-year-old female novelist (Delayed sleep phase syndrome):

She had been suffered from DSPS since her college days. She has been a typical night person and stated that she felt most alert and functioned best during the late evening and night hours of the day. She had tried several times to advance her sleep phase without success. Some times she delayed her sleep phase 2-3 h each day to adjust it to the desired cycle. This method, which was essentially similar to chronotherapy [3], was useful for adjusting her sleep phase to the desired time. But, the effect was only temporary and maintenance of the desired rhythm was difficult for her and the sleep

phase was delayed again within a few days.

At our clinic she was told to repeat the chronotherapy together with administration of 1.5mg/day methylcobalamin. She succeeded in both advancing her sleep phase and maintaining it at the desired time for more than 2 months (Fig 1-b).

3. Case 3: A 24-year college student (Irregular sleep-wake pattern):

He is a night person and has difficulty in getting up at the conventional time in the morning. As he became very alert after the early evening, he tended to sit up until very early in the morning. Sometimes he sat up all day followed by sleep which was longer than 12 h. His effort to sleep earlier than his habitual time always failed. When he visited our clinic, he was in a critical state concerning his graduation from college because of frequent absences from class. He sincerely hoped to be able to sleep at night and attend his calss during the day. We gave him methylcobalamin at a dose rate of 3.0mg each day. It was effective in consolidating his sleep during the night, although his sleep phase was still delayed (Fig 1-c).

Fig 1. Sleep diaries of patients with non-24 h sleep-wake syndrome (a), delayed sleep phase syndrome (b) and irregular sleep wake cycle (c). Ordinate and abscissa show days after start recording and time of day, respectively. Solid bars in each day indicate the period of sleep. The sleep-wake patterns are demonstrated using a double plot method to clearly present the free-running pattern.

III. MULTI-CENTER STUDY

To investigate the effect of vitamin B₁₂ on a larger group of patients with rhythm disorders, we have organized a multi-center study on this subject with cooperation of 31 facilities all over the Japanese Archipelago. Patients were recruited via nationwide or local newspapers. After publication of a scientific article describing rhythm disorders, 3985 people requested questionnaires. Based on answers to the questionnaire and the recording of their sleep-wake cycle for 4 weeks, prospective patients were referred to the nearest study facility and were interviewed for a final diagnosis. We have followed operational criteria described in ICSD [4] to evaluate sleep-wake rhythm disorders.

Finally, 132 rhythm disorders patients were identified and 61 of them were subjected to administration of methylcobalamin at dose rates of either 1.5mg or 3.0mg per day.

As shown in Table 1, an effective response to vitamin B₁₂ was seen in 54.8% of the DSPS patients and 83.4% of non-24 h sleep-wake syndrome patients. On the other hand, only one of 7 patients with an irregular sleep-wake cycle benefited from this drug. These results suggest that vitamin B₁₂ may benefit some types of sleep-wake rhythm disorders, especially the non-24 h sleep-wake syndrome, even though psycho-social factors have to be considered as also affecting the rhythm disorders in the present study.

Table 1

EFFECT OF VITAMIN B₁₂ ON SLEEP-WAKE RHYTHM DISORDERS

	DSPS	Non-24 h	Irregular	Total
Improved				
Marked	5 (11.9%)	3 (25.0%)	0 (0.0%)	8
Moderately	8 (19.0%)	6 (50.0%)	1 (14.3%)	15
Slightly	10 (23.8%)	1 (8.3%)	0 (0.0%)	11
No Effect	19 (45.2%)	2 (16.6%)	6 (85.7%)	27
Total	42	12	7	61

IV. UNDERLYING MECHANISM OF THE EFFECT OF VITAMIN B₁₂ ON THE RHYTHM DISORDERS

Although the mechanism underlying the effect of vitamin B₁₂ on the rhythm disorders is still unknown, several possibilities are conceivable as follows. First, it is possible that vitamin B₁₂ increases the retinal sensitivity to light. If an individual become more sensitive to light, he would be able to entrain more easily to the natural 24-h environment. However, our experiment using rats failed to show such an increase of light sensitivity. Secondly, rhythm disorders are possibly improved as a result of sleep facilitation by vitamin B₁₂, since Inoue et al. showed that methylcobalamin administered into the 3rd ventricle increased both non-REM and REM sleep in rats [5]. However, this fact does not seem to clarify the whole mechanism of rhythm adjustment, even though it may be partly involved in the remedy of rhythm disorder. Thirdly, shortening of the free-running rhythm caused by vitamin B₁₂ may facilitate the entrainment of disordered rhythm. Takahashi et al. suggested that chronic administration of methylcobalamin using a mini-pump caused a shortening of the free-running period in rats kept under constant darkness [6]. If the free-running period becomes shorter, the period of endogenous rhythm becomes closer to that of environmental rhythm with a 24 h period. This may consequently facilitate a human to adjust back into the conventional social rhythm. Thus, the third possibility seems to be most reasonable for understanding the effect of vitamin B₁₂ on rhythm disorders.

Then a question that naturally occurs is how vitamin B₁₂ changes the period of the endogenous clock. Accordingly, we have investigated the effect of vitamin B₁₂ on the cholinergic system, as we have previously demonstrated that carbachol, a cholinergic agent, shortens the free-running rhythm in blinded rats [7]. As shown in Table 2, methylcobalamin given subcutaneously for 3 weeks at daily doses of 500µg/rat significantly increased the content of acetylcholine determined by RIA [8] in both the frontal cortex and striatum in rats (Table 2). Thus, it is possible that vitamin B₁₂ shortens the free-running period via an increment of the cholinergic function. Such the acetylcholine content in the SCN was not increased and it took a relatively long period until a significant increase emerged in the present study, we have to be cautious to conclude that methylcobalamin exerts its effect on the rhythm disorder by increasing the cholinergic function in the SCN. However, the relationship between the cholinergic system and vitamin B₁₂ seems deserved to be investigated in order to explore the mechanism of the therapeutic effect of vitamin B₁₂ on rhythm disorders.

Table 2

EFFECT OF METHYLCOBALAMIN GIVEN FOR 7, 14 OR 21 DAYS ON ACETYLCHOLINE CONTENT (pmol/mg protein) IN THE DISCRETE AREAS OF RAT BRAIN

	Control	7 days	14 days	21 days
Frontal Cortex	155.0 ± 22.5	162.0 ± 34.3	171.0 ± 29.5	260.0 ± 98.9(*)
Hypothalamus	91.1 ± 35.3	105.0 ± 32.7	130.0 ± 59.3	123.0 ± 24.8
Striatum	449.0 ± 115.3	506.0 ± 190.4	682.0 ± 146.4(*)	775.0 ± 257.5(*)

(*) $p < 0.05$ vs control

ACKNOWLEDGEMENT

The authors are grateful to Dr. Kawashima for donating to us the anti-acetylcholine antiserum.

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