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Sleep, Serotonin, and Suicide in Japan

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Abstract This article reviews evidence supporting the hypothesis that suicide rates in Japan could be reduced by elevating serotonin levels via increasing the average duration of sleep. Seven major relevant findings were apparent in the literature: 1) Sleep loss is associated with suicide, but the direction of causality is equivocal. 2) Decreased serotonergic activity may be involved in suicidal behavior. 3) Sleep debt may decrease serotonergic activity. 4) The suicide rate in Japan has remained at a heightened level for the past 12 years. 5) The average sleep duration in Japan has decreased over the past 40 years. 6) The average sleep duration in Japan is among the lowest in the world. 7) The average sleep duration in Japan plateaued in 1995 and has been relatively stable since. From the research reviewed, two major problematic issues were apparent: 1) Most people in Japan receive inadequate sleep. 2) Individuals whose sleep is inadequate are unlikely to be sufficiently physically active to stimulate serotonergic systems to a desirable level. I propose that public health initiatives encouraging a longer duration of sleep may provide a relatively simple way of addressing the disturbing current trend in Japan. The combination of actigraph and brain serotonin level measurement could allow large population-based cohort studies to be designed, to elucidate the causal links between sleep duration, serotonin levels, and suicide rates. *J Physiol Anthropol 30(1): 1–8, 2011* http://www.jstage.jst.go.jp/browse/jpa2
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Introduction

Suicide is a complex behavior. Depression is highly prevalent among people who commit suicide (Conwell et al., 1996), but many other risk factors have also been implicated, including other health conditions (e.g., alcohol dependency, cancer), sociodemographic features (e.g., higher rates in males, the unmarried, and unemployed individuals), socioeconomic factors, and climatic factors (e.g., cold weather, insufficient sunshine, and snowfall; Nakao et al., 2008). In Japan, the number of cases of suicide increased significantly in 1998, and the suicide rate has remained high to date. There is currently no conclusive explanation for this phenomenon. In a previous paper I hypothesized that suicide rates in Japan might be reduced by elevating serotonin levels via increasing the average duration of sleep in the population (Kohyama, 2010, but see Pires et al., 2010, for a critique of this hypothesis). In accordance with my prediction, Bernert and Joiner (2007) reported that suicide attempts and completed suicide were associated with serotonergic dysfunction. They also reported that studies investigating whether sleep treatment can reduce the risk for suicidal behaviors are needed. In the present article, the key evidence in support of my hypothesis is briefly reviewed, followed by a discussion of some potential measures for reducing the rate of suicide in Japan.

Suicide and sleep

Although depression showed the strongest link with suicide, poor sleep quality increased the risk for suicide by 34% (Turvey et al., 2002). Fujino et al. (2005) showed that, among 13,259 middle-aged adults, only difficulty maintaining sleep at baseline, compared to other sleep disturbances (e.g., difficulty initiating sleep, nonrestorative sleep), significantly predicted death by suicide 14 years later. Bernert and Joiner (2007) cited these two references and noted that depression was not accounted for when examining the association between sleep and completed suicide.

Several recent studies have examined the association between sleep disturbance and suicide rates in patients with a range of psychiatric disorders, including major depression, panic disorder, and schizophrenia (Agargun et al., 1998a; Agargun and Kara, 1998b; Singareddy and Balon, 2001). Wojnar et al. (2009) conducted the first study examining the association between symptoms of insomnia and suicidal behavior over a 12-month period. Based on a sample of 5,692 American adults, it was found that chronic sleep problems were associated with a greater risk of suicide (Wojnar et al., 2009). In addition, the investigators suggested that addressing sleep problems could reduce the risk of suicidal behavior.

In a large community sample, the association between sleep and suicidal behavior was investigated in Chinese adolescents (Liu, 2004). Adolescents (n=1,362) attending school were

surveyed with a self-administered questionnaire regarding sleep patterns, sleep problems, suicidal behavior, depressive symptoms, and demographic characteristics of family members. Logistic regression analyses revealed that sleeping <8 hours at night was associated with an increased risk of suicide attempts after adjusting for age, sex, and father's occupation. Although additional longitudinal studies using objective measures of sleep duration are needed to replicate these findings and confirm a causal link, Liu's (2004) study provided an important step for understanding the association between short sleep duration and suicide in adolescents. However, it should be emphasized that the direction of causality remains equivocal. As such, it remains possible that suicidal thoughts may cause trouble sleeping rather than the converse.

In a study of sleep-deprived participants, Yoo et al. (2007) reported a heightened hyperlimbic response to negative emotional stimuli in the amygdala, associated with reduced functional connectivity with the medial prefrontal cortex. These findings lend further support to the notion that sleep loss is associated with irrational emotional behavior, including suicide.

Suicide and serotonin

Since many risk factors have been implicated in suicide (Nakao et al., 2008), it is difficult to establish direct links between suicide and specific neurotransmitters. Indeed, norepinephrine, serotonin, dopamine (Gunnell et al., 2009), CRF/cortisol, and retinoic acid (Bremner and McCaffery, 2008) are reported to be involved in affective disorders including depression, which is highly prevalent among people who die as a result of suicide (Conwell et al., 1996). However, one study found that reduced serotonin synthesis was exhibited in the prefrontal cortex of individuals who had attempted suicide compared with healthy controls (Leyton et al., 2006). This evidence further suggests a link between serotonin and suicide, in accordance with the currently proposed hypothesis (Kohyama, 2010). The association between suicide and the serotonergic system was proposed by several authors in 1992. Mann and Arango (1992) reported that alterations in the serotonergic system could be a risk factor for suicidal behavior. Linnoila and Virkkunen (1992) proposed the term 'low serotonin syndrome' as a clinical entity linked to violent suicide attempts. The potential role of the hypothalamic-pituitary-adrenal (HPA) axis must also be considered in discussing the link between serotonin and suicide, because corticosteroids may play an important role in the relationship between stress, mood changes, and suicidal behavior via an interaction with serotonin1A (5HT1A) receptors (Pompili et al., in press).

In addition to suicidal behaviors, disturbances of the lateral orbito-prefrontal circuit have been implicated in the emergence of aggressive behavior (Alexander et al., 1986). Importantly, the serotonergic system is believed to activate this circuit (Tekin and Cummings, 2002). In addition, one study examined serotonergic conditions in relation to reward prediction with both short and long time-scales (Schweighofer et al., 2008). In that study, subjects performed a 'dynamic' delayed reward choice task that required a continuous update of reward-value estimates to maximize total gain (Schweighofer et al., 2008). Using a computational model of delayed reward choice learning, the parameters governing the subjects' reward choices were estimated in low-, normal, and high-serotonin conditions. The investigators found an increase in the proportion of small reward choices, together with an increase in the rate of discounting of delayed rewards in the low-serotonin condition compared with the control and high-serotonin conditions (Schweighofer et al., 2008). This result suggests that low serotonin levels are associated with impulsivity. Interestingly, links between impulsive personality characteristics and suicidal ideation and behavior have been reported (Smith et al., 2008). In one study, higher impulsivity levels, evaluated by multiple measures, were found to be related to a greater number of previous suicide attempts (Dougherty et al., 2004). These findings indicate that serotonergic activity, especially in the prefrontal cortex, may play a role in suicidal behavior.

Sleep and serotonin

Serotonergic activity is highest during wakefulness, decreases during nonrapid eye movement sleep, and almost ceases during rapid eye movement (REM) sleep (Portas et al., 2000). It has been suggested that serotonergic cells play a role in maintaining arousal and regulating muscle tone and in regulating some of the phasic events of REM sleep (Siegel, 2004). During wakefulness, the serotonergic system is activated not only through exposure to morning light (Cagampang et al., 1993) but also through rhythmic movements, such as gait, chewing, and respiration (Jacobs and Azmitia, 1992). It is widely recognized that poor sleep habits in humans can induce mood and motivational disturbances, reduce attention, vigilance, and concentration, and increase daytime fatigue or sleepiness (American Academy of Sleep Medicine, 2005). In addition, behaviorally induced insufficient sleep syndrome is believed to be associated with the development of anergia, fatigue, and malaise (American Academy of Sleep Medicine, 2005). When people are exhausted or sleepy, they are unlikely to perform sufficient physical activity to activate serotonergic activity to a desirable level.

A critique of the hypothesis that increasing sleep may reduce suicide rates was recently published (Pires et al., 2010). In their critique, Pires et al. (2010) argue that sleep deprivation can actually increase the activity of the serotonergic system, in conflict with the notion that a lack of serotonergic activity is involved in suicide. However, the evidence cited by the authors is a study of paradoxical sleep deprivation (Machado et al., 2008), which differs substantially from total sleep debt (Kohyama, 2011). As such, the hypothesis that total sleep debt is related to suicide remains plausible. However, I strongly agree with Pires et al. that a possible relationship between sleep debt and suicide cannot be decisively attributed to a single neurotransmitter system at this point in time.

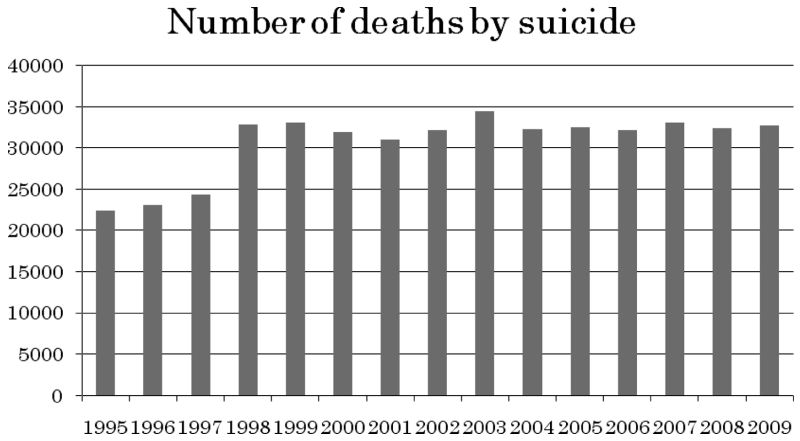

Fig. 1 Changes in the number of deaths caused by suicide in Japan by year.
(data from http://www2.ttcn.ne.jp/honkawa/2740-2.html; Honkawa, 2010a)

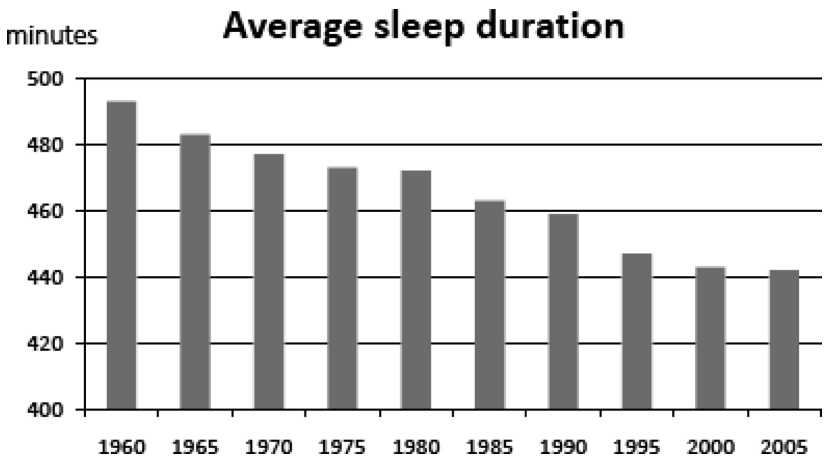

Fig. 2 Changes in the average daily sleep duration of people aged 10 years or older in Japan.
(http://www.nhk.or.jp/bunken/research/life/life_20060210.pdf; Broadcasting Culture Research Institute, 2006)

Suicide in Japan

In Japan, the annual number of cases of suicide remained steady between 1980 and 1997, ranging between 20,000 and 25,000 individuals annually (Honkawa, 2010a). In 1998, however, this number increased to 32,863 and has remained over 30,000 every year since (Fig. 1) (Honkawa, 2010a). This increase has been widely attributed to economic circumstances, with three major banks failing between November 1997 and May 1998. In accordance with the notion that economic factors are involved, most suicides in Japan occurred in the 55- to 64-year-old age-group (Honkawa, 2010b), a group that is heavily involved in the workforce and the economy. In spite of the decrease in the rate of unemployment during 2004 and 2007 (Honkawa, 2010c), however, no decrease in suicide rate was reported. No satisfactory explanation has been proposed for this maintenance of a heightened suicide rate for the past 12 years. It should be noted that the population of Japan did not change substantially during this period.

The average sleep duration in Japan has decreased over the past 40 years (Fig. 2; Broadcasting Culture Research Institute, 2006). The average sleep duration in people 10 years of age or older was reported to be 493 minutes in 1960. This figure dropped to 447 minutes by 1995, and further declined in 2000 and 2005 to 443 and 442 minutes, respectively (Broadcasting Culture Research Institute, 2006). The small decrease in sleep duration from 1995 to the present (Fig. 2) may suggest that average sleep duration in Japan has reached a minimum requirement for human survival. It should be noted that determining individual sleep needs is challenging, since sleep requirements depend on multiple factors (Carskadon and Dement, 2005). Nonetheless, it is clear that Japan has one of the lowest average sleep durations in the world (Table 1; Nielsen, 2005; Society at a Glance 2009 OECD Social Indicators, 2009; Walt Disney Studios Home Entertainment, 2008). In addition, one study reported that the average sleep duration for people aged 18–64 years in Japan was 6.4 hours in 2008 (Walt Disney Studios Home Entertainment, 2008).

Table 1 Sleep duration, suicide rate, labor productivity, and the percentage of long-time workers in several nations*

	Sleep duration (min) (Society at a Glance OECD Social Indicators, 2009)	Suicide rate per 100,000 individuals (Honkawa, 2010a)	Percentage of long-time workers (Honkawa, 2010d)**	Labor Productivity (USD, Japan productivity Center, 2010)
Korea	469	21.9	no data	46918
Japan	470	24.4	28.1	61862
Norway	483	11.4	no data	97275
Sweden	486	13.2	1.9	68025
Germany	492	11.9	5.3	69600
Italy	498	6.3	4.2	73179
Mexico	501	4.0	no data	27309
United Kingdom	503	6.4	15.5	70343
Belgium	505	18.2	3.8	80878
Finland	507	18.8	4.5	66981
Poland	508	15.2	no data	37465
Canada	509	11.3	no data	67723
Australia	512	10.8	20.0	69836
Turkey	512	no data	no data	24647
New Zealand	513	12.4	21.3	51128
Spain	514	7.8	5.8	62669
United States	518	11.0	20.0	86714
France	530	17.0	5.7	77007

* The list of nations is based on the Society at a Glance OECD Social Indicators report (2009).
**Long-time workers are persons who work 50 hours or more a week, except for Japan and the United States. In Japan and the United States, long-time workers are individuals who work 49 hours per week.

The plateauing of average sleep duration over the last several decades shown in Fig. 2 suggests that insufficient sleep remains prevalent in Japan. It is well established that insufficient sleep has a negative effect on daytime functioning (Wolfson and Carskadon, 1998; Randazzo et al., 1998; Teixeira et al., 2007), general well-being (Ohayon and Vecchierini, 2005), metabolic and endocrine function (Spiegel et al, 1999; Spiegel et al, 2005), body weight (Taheri et al., 2004), and psychomotor skills and mood (Dinges et al., 1997), in addition to the increased risk of suicide attempts mentioned above (Liu, 2004). Although difficulty in maintaining sleep has been recognized as a risk factor for suicide in Japan (Fujino et al., 2005), a recent review on suicide in Japan did not discuss this issue (Nakao et al., 2008). To the author's knowledge, the current review and the recent brief report mentioned above (Kohyama, 2010) are the first reports suggesting an association between sleep and suicide in Japan.

Japan is the only nation in the world in which >25% of employed people are categorized as long-time workers (working 50 hours or more per week; Table 1; Honkawa, 2010d). Conversely, labor productivity in Japan is below the average level of 30 industrialized nations, with the lowest value among developed nations (Table 1; Japan Productivity Center, 2010). This indicates that workers in Japan are likely to be sleep-deprived and work long hours. Consequently, they tend to exhibit poor productivity, and are likely to receive insufficient rhythmic physical activity. Further research is needed to investigate whether the serotonin levels of workers in Japan are particularly low relative to other countries.

Suicide rates in France have decreased since 1986 (Honkawa, 2010b), and the average sleep duration in France is 60 minutes longer than that in Japan (Society at a Glance 2009 OECD Social Indicators, 2009). Nevertheless, the French government launched plans to spend $9 million USD in 2007 to raise public awareness about sleep problems and the need to improve sleep (Fox news, 2007), indicating a recognition of the need for sleep in that country. In the international community, people in Japan are widely considered to be highly industrious. For most people in Japan, striving to achieve their best is an important principle, even if this comes at the expense of sleep. The time constraint produced by this situation is likely to prevent many workers from receiving a sufficient amount of active physical exercise, including rhythmic movements. This lack of exercise may further decrease serotonergic activity in the population.

Sleep, serotonin, and suicide in Japan

As reviewed above, a range of research supports the notion that a link may exist between sleep duration, serotonin levels, and suicidal behavior. So far, the role of sleep on suicide has often been discussed in terms of symptoms of depression (Agargun et al., 1998a; Agargun and Kara, 1998b; Singareddy and Balon, 2001); however, it has been suggested that maintenance of sleep is involved in suicidal behavior independent of depression (Turvey et al., 2002; Fujino et al., 2005; Bernert and Joiner, 2007). Potential links among these factors are illustrated in Fig. 3. The cultural preference of many people in Japan for work at the expense of rest could affect these links. Further research is required to determine conclusively whether an increase in average sleep duration can

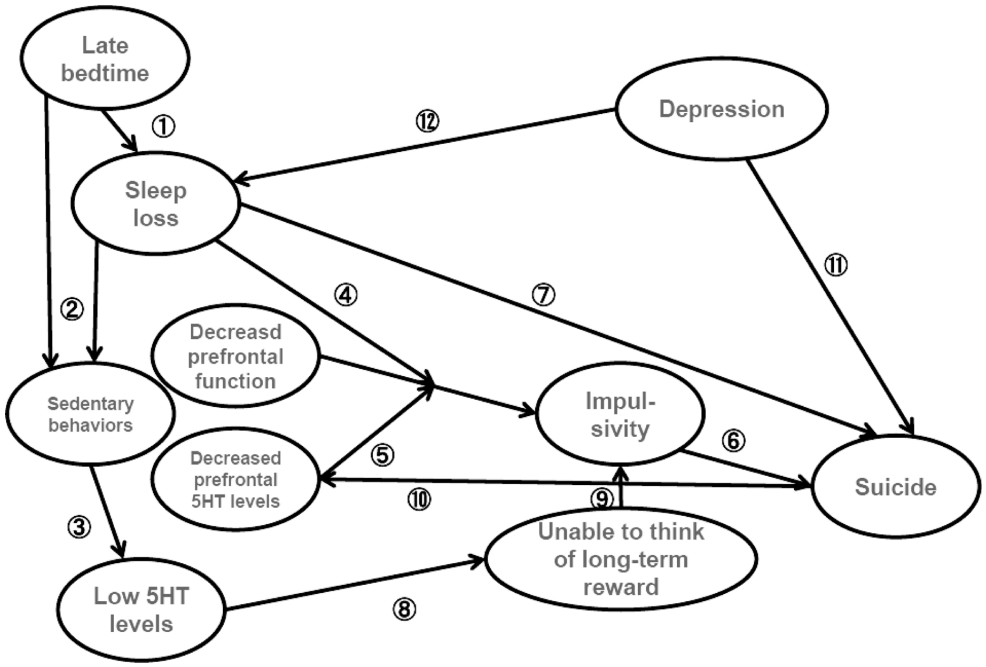

Fig. 3 Links between sleep, serotonin, and suicide.
1, 2: Kohyama, 2009; 3: Jacobs and Azmitia, 1992; 4: Yoo et al., 2007; 5: Tekin and Cummings, 2002; 6: Smith et al., 2008; 7: Liu, 2004; 8: Schweighofer et al., 2008; 9: my paraphrase; 10: Leyton et al., 2006; 11: Conwell et al., 1996; 12: Agargun et al., 1998a; Agargun et al., 1998b; Singareddy and Balon, 2001.

decrease the incidence of suicide via the elevation of serotonergic activity.

Implications

Several possibilities exist for determining whether an increase in the duration of sleep can lead to an elevation of serotonergic activity and a reduction in suicidal behavior. Since suicide is a multifactorial behavior, it is necessary to design studies that isolate the effects of a single factor while controlling for other potentially influential factors. This is a difficult challenge. In addition, adequate sleep duration is reported to vary substantially between individuals (Carskadon and Dement, 2005). Considering this individual variability, cross-sectional studies to assess suicide rates among groups of individuals with variable sleep durations may not be an appropriate approach for testing the relationship between sleep duration and suicidal behaviors. As such, a large population-based cohort design may be a good candidate to confirm the proposed hypothesis. Since the average sleep duration in Japan has been decreasing in recent years (Fig. 1), it is difficult to design studies where a study population obtains a spontaneous increase in sleep duration contrary to the current trend. Such a study would require powerful intervention to increase the duration of sleep. As such, public health initiatives encouraging people in Japan to sleep longer each night may be essential for this research to be conducted.

So far, efforts to promote the importance of sleep in the last several years have been specifically targeted at children (Hoshino et al., 2010). Young people have been targeted because >50% of children in Japan were found to go to bed at 10:00 p.m. or later (Kohyama et al, 2002; Yokomaku et al., 2008; Kohyama, 2009). In 2006, the Ministry of Education, Culture, Sports, Science and Technology began a nationwide campaign to promote a lifestyle in which people go to bed early, wake up early, and eat breakfast (2006). These campaigns are in accordance with recent findings regarding the features of the biological clock, referred to collectively as 'sleep hygiene' (American Academy of Sleep Medicine, 2005) or 'sleep health' (Table 2). The basic principles of sleep health are exposure to the morning light and avoidance of nocturnal light, which are the essential factors for maintaining biological clock function (Kohyama, 2008). Interestingly, the daily sleeping habits of children have improved since the implementation of this campaign. However, adult sleep habits in Japan have not been altered (Fig. 2; Nielsen, 2005; Society at a Glance 2009 OECD Social Indicators, 2009; Walt Disney Studios Home Entertainment, 2008). The majority of adults in Japan continue to choose work over sleep. To more success-

Table 2 Healthy sleep habits (sleep health practice/treatment: SHP/T)

1. Increase exposure to morning light.
2. Engage in physical activity during the daytime.
3. Sleep in the dark during the night (i.e., turn off all artificial lighting).
4. Eat regular meals.
5. Avoid substances that disturb sleep (e.g., caffeine, alcohol, nicotine).
6. Avoid excessive media exposure (e.g., video games, computers, television).

fully promote the notion of the importance of increasing sleep duration, a greater understanding of basic sleep health, supported by recent progress in neuroscience research (Table 2), is an important step.

In Japanese, reading a book to another person is called 'yomikikase': 'yomi' means to read, and 'kikase' means to have someone listen. Kawai et al. (2008) reported that parents who engaged in yomikikase communicated more effectively with their youngsters compared with those who did not engage in yomikikase. Interestingly, reduced serotonergic activity is reported to be a disadvantage in attaining high social status (Raleigh et al., 1991). Disturbances of the lateral orbitoprefrontal circuit have also been implicated in deficits of sociability (Alexander et al., 1986), and the serotonergic system is known to activate this circuit (Tekin and Cummings, 2002). There is evidence that yomikikase may be involved in activating serotonergic activity. A recent study reported that yomikikase activated the limbic structures of child listeners but also affected the neuronal activity of readers (Haji et al., 2007; Taira, 2009). One study compared frontal cerebral blood flow using functional near-infrared spectroscopy, examining the difference between yomikikase and simple book-reading in mothers, and found that frontal cerebral blood flow of mothers was greater during yomikikase. This preliminary result did not directly confirm the elevation of serotonergic activity in the brain, and did not find activation of the limbic system of adult listeners or elevation of frontal cerebral blood flow in fathers during yomikikase. These questions require further investigation. Measures to increase the practice of yomikikase may affect multiple variables. For example, encouraging parents to perform yomikikase may cause them to come home earlier, which would cut down their working hours and potentially ameliorate problems associated with sleep loss, including the risk of suicide. It should also be noted that yomikikase has also been found to be popular among adults for their own pleasure, not only as listeners but also as readers (Kikaseya, 2010). Increasing the prevalence of yomikikase would thus be predicted to promote public health, encouraging people in Japan to increase their average sleep duration.

Methods for assessing brain serotonergic activity can be roughly divided into indirect and direct approaches. In an indirect approach, because morning light and rhythmic physical activity are effective for stimulating the serotonergic system, serotonergic activity in the brain could be assessed indirectly through calculating the amount of morning sunlight exposure and rhythmic physical activity. Current technology is sufficient for the development of devices enabling this type of measurement without difficulty (e.g., pedometers built into cell phones). Relevant to a direct measurement approach, augmented brain serotonin was recently found to cross the blood-brain barrier via the serotonin transporter in rats (Nakatani et al., 2008). This finding indicates that it may soon be possible to assess brain serotonin levels from blood samples. In addition, blood glucose level can now be obtained without taking a blood sample (Yamakoshi et al., 2009). Thus, methods enabling direct, noninvasive measurement of brain serotonin levels are likely to be available in the near future.

The actigraph is a small, wrist-worn device that contains an accelerometer to monitor the number of wrist movements per measurement period (Ancoli-Israel et al., 2003). Scoring algorithms are used to identify sleep or wake states from activity counts over relatively long periods (Ancoli-Israel et al., 2003). The combination of an actigraph and equipment for measuring brain serotonin level would enable large population-based cohort studies to elucidate the causal links between sleep duration, physical activity, serotonin levels, and suicide rates.

Conclusion

There is clear evidence that sleep, serotonin levels, and suicide are linked, although the direction of causation requires clarification. Internationally, Japan has one of the shortest average sleep durations and one of the highest suicide rates. Implementing public health initiatives encouraging people in Japan to get more sleep may be a relatively simple means of addressing disturbing current trends in sleep duration and suicide rates in Japan. Yomikikase could play a valuable role in these initiatives. The combination of the actigraph and equipment for measuring serotonin levels in the brain could allow the design of large population-based cohort studies to elucidate the direction of causation in the relationships between sleep duration, serotonin levels, and suicide rates.

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