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Sleep, Serotonin, and Suicide

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ABSTRACT

The author hypothesizes that sleep loss associated with a decrease in serotonergic activity plays a significant role in attempted suicide. Recent research has emphasized the role of the economic recession on the occurrence of suicide, but with no attention paid to possible biological aspects. In this brief review, the association between sleep, the serotonergic system, and suicide is initially introduced. Then, with consideration of recent research, a hypothesis regarding the occurrence of suicide is proposed. Finally, based on that hypothesis, three factors possibly germane to reducing suicides (sufficient sleep duration, activation of the serotonergic system, and activation of the prefrontal cortex) are discussed.

Keywords: Economic Crisis; Prefrontal Cortex; C-Fiber; Yomikikase; Dakko

1. Introduction

Suicide is a complex behavior. Although depression is highly prevalent among people who commit suicide [1], many other risk factors have been implicated, including other health conditions (e.g., alcohol dependency, drug, dependency, cancer), sociodemographic features (e.g., being male, unmarried, unemployed), and climatic factors (e.g., cold weather, insufficient sunshine, snowfall) [2].

The author proposes that sleep loss may also play a significant role in attempted suicide, associated with a decrease in serotonin (5-hydroxytriptamine; 5-HT) activity [3,4]. A study emphasizing the role of the economic recession on the occurrence of suicide in the UK has been published [5]. However, that study lacks a biological viewpoint [6]. In this brief review, the association between sleep, 5-HT, and suicide is initially introduced. Then, a novel hypothesis regarding the occurrence of suicide will be proposed.

2. Suicide and Serotonin

It is difficult to establish direct links between suicide and specific neurotransmitters. However, norepinephrine, 5-HT, dopamine [7], corticotrophin-releasing factor (CRF)/cortisol, and retinoic acid [8] are reported to be involved in affective disorders including depression, which is highly prevalent among people who die as a result of suicide [1].

An association between suicide and hypofunction of the 5-HT system was proposed by several researchers in 1992. Therefore, all articles on suicide cited in this manuscript have been published in 1992 or after this year. Linnoila and Virkkunen [9] used the term 'low serotonin syndrome' as a clinical entity linked to violent suicide attempts. Mann and Arango [10] reported that alterations in the 5-HT system could be a risk factor for suicidal behavior. In 1995, Arango *et al*. [11] found an increase in 5-HT1A receptors in the ventrolateral prefrontal cortex (vlPFC) and a decrease in serotonin transporters in the vlPFC of suicide brains. The increase in 5-HT1A receptors in the vlPFC was interpreted as the result of up-regulation due to hypofunction of the 5-HT system. They concluded that suicide victims have an abnormality in the 5-HT system involving predominantly the vlPFC, and hypothesized that 5-HT dysfunction in this brain region contributes to the risk for suicidal behavior.

The vlPFC has been implicated in behavioral inhibition and impulsivity [12,13]. Damage to this area causes an inability to change impulsive aggressive behavior, resulting in poor anger management [12]. If such behavior is directed inwardly instead of outwardly at others, the result may be suicide [12]. Although in mice, after the consumption of a moderate dose of alcohol, Chiavegatto *et al*. [14] reported a regionally selective and significant reduction of all 5-HT receptor subtype transcripts, except for 5-HT3, in the PFC of those who showed escalated aggression. Indeed, whether the anti- aggressive effects of 5-HT manipulations are associated with increased or decreased 5-HT transmission as a common neurobiological mechanism remains to be determined [14]. Leyton *et al*. [15] found that reduced 5-HT synthesis was exhibited in the PFC of individuals who had attempted

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suicide, compared with healthy controls. Hypofunction of the 5-HT system in the PFC is likely to be involved in attempted suicide.

Because 5-HT innervation to the PFC arises predominantly from the brainstem dorsal raphe nucleus (DRN), interest has been directed toward the DRN of suicide victims. Stockmeier *et al*. [16] reported more 5-HT1A binding in depressed suicides vs. controls in the ventrolateral and dorsal subnuclei of the DRN. The 5-HT1A receptor has been classified functionally as an inhibitory autoreceptor because the firing rate of 5-HT neurons in the DRN is inhibited by the direct application of a 5-HT1A receptor agonist into the DRN [17]. Thus, Stockmeier *et al*. [16] interpreted the observed increase in presumably inhibitory 5-HT1A receptors in the DRN of depressed suicide victims as possibly providing pharmacological evidence for diminished activity of 5-HT neurons in those subjects. Consistent with that finding, Arango *et al*. [18] found higher 5-HT1A receptor cross-sectional binding in the rostral DRN in depressed suicides compared with controls, and hypothesized that the rostral elevation of DRN 5-HT1A autoreceptor binding in depressed suicides was functionally related to their previous finding of more 5-HT1A binding in the ventral and lateral PFC [11]. They reasoned that an excess of autoreceptors would tend to lower the firing rate of 5-HT DRN neurons and reduce 5-HT release in the PFC, resulting in the up-regulation (increase) of 5-HT receptors in the PFC.

A potential role of the hypothalamic-pituitary-adrenal axis must be considered in the link between 5-HT and suicide, given that corticosteroids may play an important role in the relationship between stress, mood changes, and suicidal behavior via an interaction with 5-HT1A receptors [19]. It should be noted that CRF mobilizes the organism for response to stressors and also stimulates the central nervous system to respond to environmental challenges [20]. Waselus *et al*. [21] suggested that CRF has both direct and indirect effects on 5-HT neurons in the DRN and further implicated GABA as a primary mediator by which CRF and stressors alter the activity of the DRN-5-HT system. An indirect effect via stimulation of inhibitory GABA synaptic transmission may primarily produce the inhibition of 5-HT DRN neurons by CRF [22]. Neurosecretory neurons of the paraventricular nucleus (PVN) of the hypothalamus synthesize CRF [23]. However, it should be noted that the PVN projects only to a limited number of areas in the midbrain, including the DRN [24]. The source of CRF projected to the DRN remains to be determined.

Disturbances of the lateral orbito-prefrontal circuit have also been implicated in the emergence of aggressive behaviors [25]. Importantly, the 5-HT system is believed to activate this circuit [26]. Schweighofer *et al*. [27] examined 5-HT conditions in relation to reward prediction with both short and long timeframes. They 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 5-HT condition compared with the control and high 5-HT conditions. This suggests that low 5-HT levels are associated with impulsivity. Interestingly, links between impulsive personality characteristics and suicidal ideation and behavior have been reported [28]. Indeed, higher impulsivity levels, evaluated by multiple measures, were found to be related to a greater number of previous suicide attempts [29]. In addition, when subjects learned to act to obtain large future rewards while incurring small immediate losses, the dorsolateral PFC, inferior parietal cortex, DRN, and cerebellum were activated [30]. These findings indicate that decreased 5-HT activity, especially in the PFC, may play a role in suicidal behaviors.

3. Serotonin and Sleep

Research shows that chronically sleep-restricted rats have a blunted temperature response to direct stimulation of 5-HT1A receptors with a 1A agonist [31, 32]. These experiments indicate that chronic sleep restriction causes a gradual and persistent desensitization of the 5-HT1A receptor system. Novati *et al*. [33] showed that chronic sleep restriction results in decreased sensitivity of 5-HT1A receptors, assessed through pituitary response elicited by direct pharmacological stimulation with a 5-HT1A agonist. It is well-known that levels of 5-HT are higher during wakefulness than during sleep. Novati *et al*. [33] raised the possibility that chronic sleep restriction and prolonged wakefulness lead to overstimulation and ultimately downregulation of 5-HT receptors. However, it should also be noted that acute sleep deprivation [34] or rapid eye movement (REM) sleep deprivation [35] can activate the 5-HT system.

5-HT activity is highest during wakefulness, decreases during non-REM sleep, and almost ceases during REM sleep [36]. During wakefulness, the 5-HT system is activated not only through exposure to morning light [37] but also through rhythmic movements, such as gait, chewing, and respiration [38]. 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 [39]. In addition, behaviorally-induced insufficient sleep syndrome is believed to be associated with the development of anergia, fatigue, and malaise [39]. When people are exhausted or sleepy, they are unlikely to perform sufficient physical activity to promote 5-HT activity to a desirable level.

4. Sleep and Suicide

In addition to depression, poor sleep quality has been found to increase the risk for suicide [40]. Fujino *et al*. [41] showed that among 13,259 middle-aged adults, only difficulty maintaining sleep at baseline, compared with other sleep disturbances (e.g., difficulty initiating sleep, nonrestorative sleep) significantly predicted death by suicide 14 years later. Bernert and Joiner [42] cited these two studies and noted that depression was not accounted for when examining the association between sleep and completed suicide.

Several 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 [43-45]. Wojnar *et al*. [46] found that chronic sleep problems were associated with a greater risk of suicide. In addition, the investigators suggested that addressing sleep problems could reduce the risk of suicidal behavior.

In China [47], 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. That study provided an important step in 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 is possible that suicidal thoughts may cause trouble sleeping rather than the converse.

In a study of sleep-deprived participants, Yoo *et al*. [48] reported a heightened hyper-limbic response to negative emotional stimuli in the amygdala, associated with reduced functional connectivity with the medial PFC. These findings lend further support to the notion that sleep loss is associated with irrational emotional behavior, including suicide.

Finally, recent meta-analysis using electronic databases for years 1966-2011 [49] supports that sleep disturbances in general, as well as insomnia and nightmares individually, appear to represent a risk factor for suicidal thoughts and behavior.

5. Suicide and the Economy

Suicides tend to increase in hard economic times, and there is evidence of a rising number in Europe [50] and in Greece [51] as people have lost their jobs and struggle to support themselves and their families, although an argument has been raised against a causal link [52]. Research by Barr *et al*. [5] suggests that the same pattern is now visible in the UK. The suicide rate had been dropping steadily in the UK for 20 years before the recession hit. However, in 2007-2008 it rose by 8% among men and 9% among women. Barr *et al*. investigated these statistics to establish whether the recession was the cause. They looked at information on suicides in 93 regions from the National Clinical and Health Outcomes Database for the decade from 2000-2010, and also examined, from the Office for National Statistics, the numbers of unemployed people claiming benefits. They found that the suicide rate among men rose by 1.4% for every 10% increase in unemployment. According to their analysis, between 2008 and 2010, 846 more men ended their life than would have been expected had the downward trend continued; the corresponding number for women was an extra 155 suicides. On average, male unemployment rose by 25.6% in each of those years, while the male suicide rate rose by 3.6% each year. When male employment rates rose briefly in 2010, the suicide rate dropped slightly. They concluded that unemployment is a particular risk factor for suicide.

A similar trend between suicide rate and unemployment rate as reported in Europe, Greece, and the UK was observed in Japan between 1988 and 1997, and from 1998 to 2000 [53,54]. However, neither the drop in unemployment rate (2004-2007) nor its increase (2007-2009) affected the number of suicides in Japan after 2000 (**Figure 1**) [53,54]. No one has been able to explain the observed relationship between rates of unemployment and suicide before 2000, and the lack of relationship after 2000. It should be noted that the annual number of suicide cases in Japan remained steady between 1980 and 1997, ranging between 20,000 and 25,000 individuals [53]. However, in 1998, this number increased to 32,863 and has remained over 30,000 for the past 14 years. Two possible explanations are proposed for this change in number of suicides in Japan and the lack of relationship between unemployment and suicides after 2000. One is that the unemployment rate does not affect the suicide rate when either the number of suicides or the unemployment rate increases beyond a certain level. The other possibility is that other factor(s) might affect the relationship between number of suicides and unemployment rate. Although further data from many other regions are needed to confirm these possibilities, in support of the latter, the author has observed unique characteristics in Japan.

6. Sleep, Serotonin, and Suicide

Japan is the only nation in the world in which >25% of employed people are categorized as long-hour workers (working 50 hours or more per week) [55]. Conversely, labor productivity in Japan is below the average level of 30 industrialized nations, with the lowest value among

developed nations [56]. This indicates that workers in Japan are likely to be sleep-deprived and work long hours. In addition, Japanese people devote little time to themselves [55]. As a result, Japan is one of the most sleepless countries, and average sleep duration has continuously decreased for at least the past 50 years. The average sleep duration of people in Japan age 10 years and older was 493 minutes in 1960 and 434 in 2010 [57]. It should be noted that the average sleep duration in 2009 reported by the OECD was 503 minutes in the UK and 470 minutes in Japan [55].

As discussed in previous sections, suicide and 5-HT, 5-HT and sleep, and sleep and suicide have mutual relationships. However, papers discussing suicide in relation to economic crisis have not referred to biological aspects. Here, it is hypothesized that financial crisis plays a significant role in the occurrence of suicide when sleep duration is preserved, while it fails to affect suicide occurrence when sleep duration decreases below a certain level, as determined by biological necessity. The biological necessity of sleep may be regulated by 5-HT activity. As mentioned, after 2000, neither the drop in rate of unemployment (2004-2007) nor its increase (2007-2009) affected the number of suicides in Japan (**Figure 1**). Sleep duration as measured after 2000 might have been at a level low enough that economic conditions did not exert an effect on occurrence of suicide. According to **Figure 1**, 442 minutes might be that value, although calibration is needed to compare that data with OECD data [55].

The schematic potential link between sleep and suicide with hypofunction of the 5-HT system is shown in **Figure 2** [1, 4, 10 - 15, 20 - 22, 26 - 29, 31 - 33, 37, 38, 43 - 45, 47, 48, 58, 59].

7. Preventing Suicides

According to the previous discussion, three factors are proposed relevant to preventing suicides: 1) sufficient sleep duration; 2) activation of 5-HT activity; and 3) activation of PFC.

Regarding sleep duration, it is difficult to specify a minimum requirement because sleep necessity can differ individually [60]. However, 442 minutes per night has been proposed from data obtained in Japan. Human beings are diurnally active; thus, their wakefulness should be highest in the morning [61]. If one feels no sleepiness in the morning, sleep duration is considered sufficient. Five basic principles are proposed for securing sufficient sleep (**Table 1** [59]).

Young [62] proposed four nonpharmacologic methods of raising brain 5-HT: 1) positive (happy) mood induction; 2) exposure to bright light; 3) exercise; and 4) a tryptophan-enriched diet. Arita [12] proposed three factors to activate the 5-HT system: rhythmic movements, solar irradiation, and grooming. In addition, he posited that the time from birth to age 6 is an extremely important period for postnatal development of the brain 5-HT system. He stressed that rhythmic movements and solar irradiation from ages 3 - 6 years clearly activate 5-HT neurons. Finally, Arita noted that grooming is the third factor in activating 5-HT neurons. He argued that carrying a baby on the back or in the arms is regarded as a grooming action between mother and child, and these

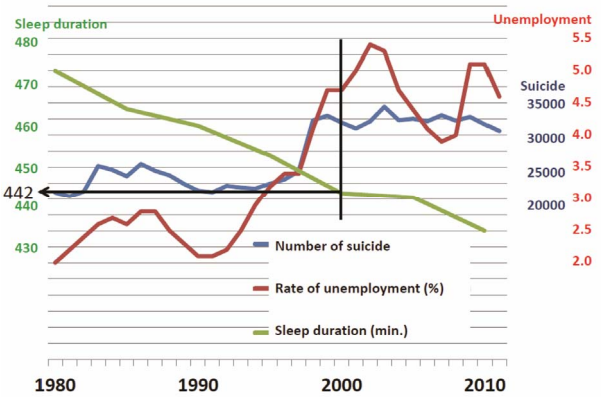

Figure 1. Change in number of suicides, unemployment rate, and sleep duration in Japan.

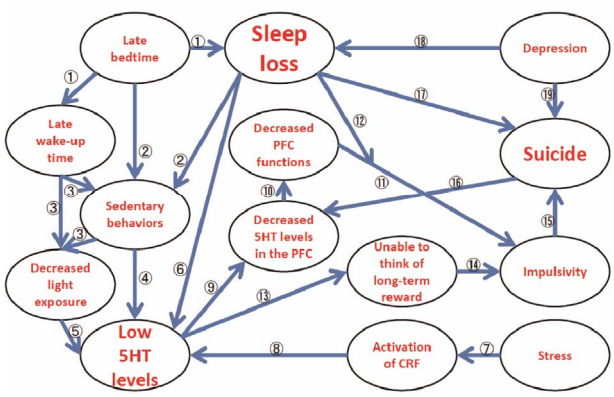

Figure 2. The schematic potential link between sleep and suicide with hypofunction of the serotonergic system. Arrows and supported references are as follows: ① 58; ② 59; ③ 12, 13; ④ 38; ⑤ 37; ⑥ 31 - 33; ⑦ 20; ⑧ 21, 22; ⑨ 10, 11; ⑩ 14; ⑪ 26; ⑫ 48; ⑬ 27; ⑭ 4; ⑮ 28, 29; ⑯ 15; ⑰ 47; ⑱ 43 - 45; ⑲ 1.

Table 1. Five principles of sleep health.

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) and excessive media exposure (e.g., video games, computers, television).

actions lead to activation of the brain 5-HT system in both mother and child. Interestingly, the level of 5-HT in the rat PFC during various types of grooming behaviors has been measured using the microdialysis method, and 5-HT levels were found to be significantly increased during induced grooming [63]. Atonia during non-REM sleep [64-66] has been preliminarily proposed as a way to assess brain 5-HT activity in humans [67].

Grooming might also be implicated in activity of the PFC. This behavior often involves tactile stimulation. In 2009, Löken *et al*. [68] reported that during soft brush stroking, low-threshold unmyelinated mechanoreceptors (C-tactile), but not myelinated afferents, responded most vigorously at intermediate brushing velocities (1 - 10 cm /second), which were perceived by subjects as being the most pleasant. According to Nagi *et al*. [69], a class of unmyelinated fibers in the human hairy skin, known as C-tactile (CT) fibers, responds to innocuous mechanical stimulation. The response properties of CT fibers have been described using a limited range of stimuli—most notably slowly moving, low-force, mechanical stimuli such as finger stroking and soft brushing [68]. Neuroimaging studies have demonstrated that CT-mediated inputs project onto the insular cortex [70]. Recently, a direct contrast of the blood-oxygenation-level-dependent response to gentle brushing of the arm and palm revealed the involvement of a network of brain regions, in addition to the posterior insula, during CT-targeted affective touch to the arm [71]. This network included areas known to be involved in social perception and social cognition, including the right posterior superior temporal sulcus and the medial PFC/dorsoanterior cingulate cortex. Activation of CT fibers might activate the social brain [72] as well as the PFC. Although mutual involvement between the 5-HT system and this CT fiber-mediated sensory system has not been determined, favorable effects of a sort of grooming, or dakko, on hypoactivity of the 5-HT system have been proposed [73,74]. An older generation Japanese pediatrician [75] says that ‘‘Holding a baby in your arms (“dakko” in Japanese) is the most effective tranquilizer for the baby.” Although therapeutic touch is now receiving attention as a method to manage anxiety disorders including depression [74], dakko is a typical daily behavior that involves direct contact between caretakers and youngsters.

In my previous paper [4], the potential role of *yomikikase* in activating the frontal brain area was introduced. Yomikikase is a Japanese word that means reading a book to another person. Yomi means to read, and kikase means to have someone listen. Yomikikase reportedly activates the limbic structures of child listeners and increases frontal cerebral blood flow, measured by functional near-infrared spectroscopy of readers [76,77]. Encouraging parents to engage in yomikikase might facilitate them coming home earlier, which would reduce their working hours and potentially ameliorate problems associated with sleep loss, including the risk of suicide. However, the exact area in the PFC that is activated during yomikikase has not been clarified. Dara *et al*. [78] reported that the functional MRI signal changes in the dorsolateral part of the PFC correlated with working memory load. The effects of yomikikase or the training of working memory on the function of vlPFC are yet to be determined.

8. Conclusion

Social conditions indispensably affect mental status and might produce alterations in human central nervous system environments. Not only 5-HT but also social conditions can affect occurrence of suicide. In addition, 5-HT activity might be affected by the process of growing up. We should explore varied views in an effort to elucidate causes of suicide and develop ways to prevent this tragedy.

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