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PREFACE

Beautiful hypothesis and an ugly little fact

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Twelve years have already passed since *Sleep and Biological Rhythms* (SBR) was launched. Fortunately, the number of submissions to SBR has rapidly increased in the past several years. We have received a number of good manuscripts, far more than we have been able to publish. For example, last year (2014) 164 manuscripts were submitted from 25 countries. The most submissions came from Japan (40), Turkey (28) and China (24). Since SBR is an official journal not only of the Japanese Society of Sleep Research, but also of the Asian Sleep Research Society, these figures are reasonable and expectable. Furthermore, in 2014 we published six Review Articles, 21 Original Articles, four Short Papers, three Case Reports, two Letters to the Editor and one Editorial. The acceptance rate is approximately 23%. The 5-Year Impact Factor was 1.035 in 2013. Recently, we decided to increase the number of SBR pages from 320 to 400 per year with the aim of publishing more manuscripts.

SBR emphasizes the periodical aspect of sleep as implied by the name of the journal. To understand sleep, we should regard it not as a single physiological event, but as a sequence of events, namely sleep and wakefulness. Sleep is affected by the preceding wakefulness and succeeding wakefulness is influenced by the preceding sleep. On the other hand, a sleep and wakefulness cycle in mammals is well known to be controlled by the circadian pacemaker located in the hypothalamic suprachiasmatic nucleus. It was more than 50 years ago that the sleep and wakefulness cycle was found to spontaneously desynchronize from the circadian body temperature rhythm, suggesting at least two different oscillation mechanisms in humans (Aschoff, 1962). Under internal desynchronization, the sleep-wake cycle showed either a shorter (approximately 17 h) or longer (approximately 33 h) periodicity than the circadian temperature rhythm (24.5 h). Several mechanisms have been proposed to explain internal desynchronization. Among them, the most beautiful hypothesis was formally proposed some 30 years ago, called the two process model (Daan *et al*. 1984). The hypothesis assumes two processes: a self-sustained circadian process and an hour-glass process, which is processed by something increasing monotonously during wakefulness and declining exponentially during sleep. The hour-glass process is often called a homeostatic process. But in my opinion, the other terminology may lead to misunderstanding, since we are still ignorant of the physiology which is controlled to be constant by the homeostatic process. Regardless, the two process model explains internal desynchronization, circabidian (approximately 48 h) rhythm and the relation between the time of sleep deprivation and the length of following recovery sleep. However, the two process hypothesis is still not supported by biological experiments. One of the major reasons for the present situation is a lack of an adequate animal model for human sleep and wakefulness, which is characterized by internal desynchronization, circabidian rhythm, non-photic entrainment and consolidated sleep and wakefulness. These characteristics are unique to humans and, to my knowledge, have never been demonstrated in experimental animals such as rats and mice except for non-photic entrainment by feeding.

Methamphetamine, a central stimulant, is demonstrated to mimic human sleep and wakefulness in terms of the abovementioned four characteristics when chronically administered by dissolving in drinking water in rats and mice. The mechanism underlying methamphetamine-induced internal desynchronization seems to be an independent oscillator called Methamphetamine-induced Oscillator (MAO) or Methamphetamine Sensitive Circadian Oscillator (MASCO). Methamphetamine is a stimulant of the central dopaminergic neurons. Recently, circadian rhythms in the clock gene *Per2* expression in the several dopaminergic structures of the rat brain were reported to be reorganized by methamphetamine and run parallel with desynchronized behavior rhythms (Natsubori *et al*. 2014). The findings support a two-oscillator model, an alternative hypothesis for the human sleep-wake cycle, which was proposed many years ago.

Hypotheses are useful to understand a complex phenomenon with a simple principle and to make testable predictions. But a tragedy is "a beautiful hypothesis slain by an ugly little fact" (Thomas Henry Huxley).