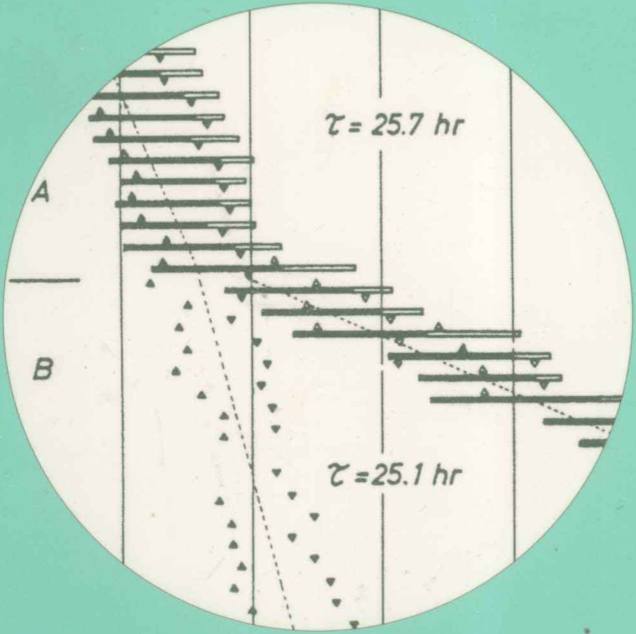
Zeitgebers, Entrainment and Masking of the Circadian System



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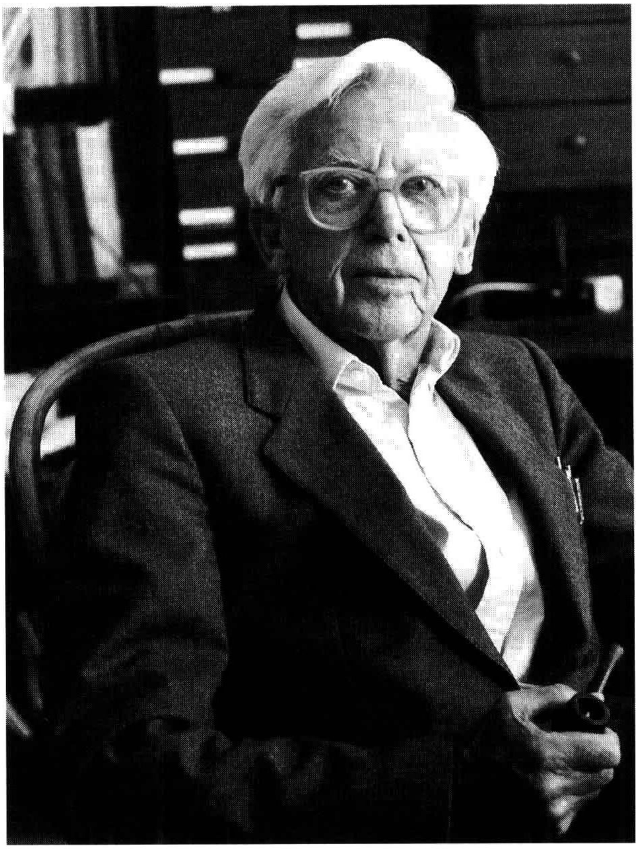

Professor Jürgen Aschoff

Dedication

— To the Memory of Professor Jürgen Aschoff —

It is his energy which we are mostly impressed and inspired. It is his humor which relaxes and attracts all of us. And it is his generosity to which we owe what the Sapporo Symposium is today. We never forget his enthusiasm and curiosity.

Herr Professor Jürgen Aschoff, leben Sie wolh!

Ken-ichi Honma

Jürgen Walther Ludwig Aschoff (1913–1998)

Jürgen Aschoff was born in January 1913 in Freiburg/Br Germany as a son of Ludwig and Clara Aschoff. He graduated from University of Freiburg/Br School of Medicne and became a research associate at the Institute of Physiology, University of Göttingen. In 1944, he got "Habilitation in Physiologie" in University of Göttingen and promoted to a professor of physiology. Later, he became a scientific member of the Max-Planck-Gesellschaft and had the initiative as the director at the Max-Planck-Institut für Verhaltensphysiologie in Seewiesen and Andechs. In 1981, he retired from the Max-Planck-Institute, but continued his scientific activity untill the last moment of his death on 11th October in 1998.

He was an honorary member of the Italian Society of Experimental Biology, of the American Ornithologists' Union, of the British Ornithologists' Union, of the German Physiological Society, of the Deutsche Ornithologen-Gesellschaft. He was given with Dr. Med. H.C. by University of Giessen in 1982 and by Hokkaido University in 1993, and awarded with Feldberg Prize.

His major contribution to academia is thermoregulation, especially convective heat transfer and cold defense mechanisms in humans, and biological rhythms with emphasis on circadian rhythms. In the former field, he developed the concept of core and shell in homeothermic organisms, and in the latter, he analysed formal properties of circadian rhythms and their synchronization by environmental periodic factors (zeitgebers). He conducted long-term studies with human subjects during temporal isolation in underground isolation units and described changes in the internal temporal order and the dynamics of the sleep-wake cycle and other rhythms under a variety of environmental conditions.

Preface

The 8th Sapporo Symposium for Biological Rhythm was held in August 1999. This symposium was specially designed to commemorate Jürgen Aschoff who passed away in 1998. Jürgen Aschoff was one of the founders of the Sapporo Symposium and participated in more than several times to encourage young scientists despite of a long distance and of his age. In 1993, the Hokkaido University bestowed an honorary degree of medicine upon him for his extraordinary contribution to education.

The 8th Sapporo Symposium was a joint meeting with the International Symposium of the Ministry of Education, Science and Culture of Japan. The symposium was consisted of 4 lectures and 4 symposiums (Clock Genes, Zeitgebers and Entrainment, Complexity of Circadian System, New Direction). The Honma Prize Winner's Lecture was given by Dr. Steve Kay, and Dedications to Jürgen Aschoff by Drs. Serge Daan, Tsutomu Hiroshige and Patricia DeCoursey. Two of the topics we selected for symposiums came from a monograph edited by Jürgen Aschoff, 'Zeitgeber, Entrainment and Masking: Some Unsettled Question' (1982). This idea came up not only because they were the issues addressed by Jürgen Aschoff, but also because I thought we really needed these ways of thinking after discovery of many clock genes.

The proceeding volume of 8th Sapporo Symposium entitled "Zeitgebers, Entrainment and Masking of the Circadian System" contained 19 papers and discussions for each. Among them, noteworthy are the three papers which deal with the life and science of Jürgen Aschoff. They are invaluable sources for the biography of Jürgen Aschoff which will be written in future. The book is also highlighted by the paper of Dr. Steve Kay, the 7th Honma Prize Winner. The title of prize will be changed to the Aschoff-Honma Prize from the next Sapporo Symposium.

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December 2000

Ken-ichi Honma, M. D., Ph. D.
Chairman of Sapporo Symposium

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Contents

Plenary Article

Dr. Steve A. Kay was born in October 1959 as a citizen of UK. He studied biochemistry in University of Bristol and received his Ph.D in 1984. He became an assistant professor in the Rockefeller University and later in University of Virginia. In 1995, he promoted to an associate professor with tenure and became a director in Advanced Cellular Imaging Faculty, University Virginia. One year later, he moved to the Scripps Research Institute and became a professor of cell biology in 1998.

Dr. Steve Kay has made major contribution to our understanding of the genetic and molecular mechanism of circadian clock. In his early studies, he analyzed the rice phytochrome and wheat Cab genes which introduced him to the field of circadian rhythm. He developed a new technique for monitoring circadian rhythmicities using a bioluminescence reporter-gene, firefly luciferase, and found circadian clock mutant in Arabidopsis. More recently, he becomes involved also in drosophila and mammalian circadian clocks. By these achievements, Dr. Steve Kay proved himself as an outstanding and ambitious scientist.

Toward Understanding Circadian Rhythms

Steve A. Kay and Karen Wager-Smith

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Our endogenous circadian clock gives rise to daily fluctuations in biochemistry, physiology, and behavior. The clock is genetically determined but responds to changes in the environment in order to synchronize its rhythm precisely to the light-dark cycle. A circadian clock or oscillator is exhibited by organisms from prokaryotes to humans, and is of both biological and clinical importance. For example, the optimal timing for administration of certain drugs depends on the circadian cycle. Jet lag and shift work disrupt circadian function. Some types of insomnia appear to be due to impairments in circadian timekeeping. Even some psychiatric conditions may be related to circadian abnormalities. Advances in exploiting and manipulating clock function and understanding its pathology will be aided by knowledge of the timekeeping molecules and how they work. In the last several year, extensive progress has been made in circadian research. It has been discovered that the genes involved in the clock and their functions are conserved between invertebrates and mammals, so that insight into the human clock can be gleaned through research in tractable experimental organisms. Our view of the anatomical location of the clock is being challenged. Moreover, the biochemical mode of action of many of the clock's component molecules has been demonstrated for the first time.

There are three aspects of circadian biology (Fig. 1). Like a setting pin on a pocket watch, the input consists of features from the environment that can reset the central oscillator. The most potent of these is light, but temperature, social cues, and our own activity can also input in some cases. The central oscillator consists of the timekeeping proteins that constitute the gears of the watch. These molecules work together to generate a 24 hour rhythm. Subtle changes in the amino acid sequence of any one of these proteins can cause the central oscillator to speed up or to slow down. If any one of these proteins is missing, the watch grinds to a halt and rhythmicity of all outputs cease. The outputs, like the hands on the watch, are the things that the oscillator regulates such as plasma hormone levels, core body temperature, and the desire for sleep.

Adaptation to the Earth's 24 hour day-night cycle is an obvious and stringent

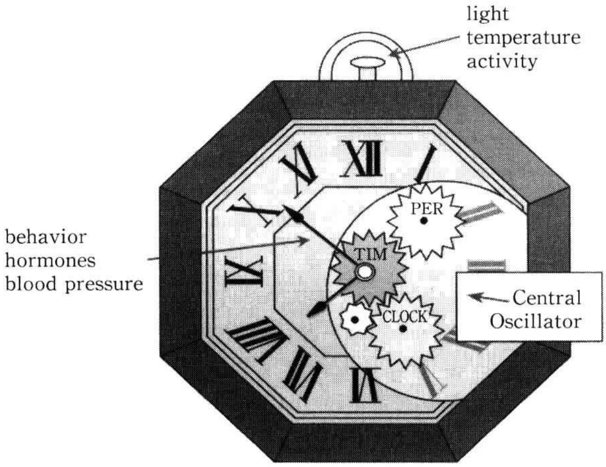

Fig. 1 The endogenous circadian oscillator is analogous to a pocket watch. The setting pin is the pathway through which light and other features of the environment reset the oscillator, synchronizing it to local time. The gears of the watch represent the central oscillator component proteins which work together to generate a 24 hour timepiece. The teeth of each gear are their specific amino acid sequences, changes in which can speed up, slow down or destroy clock function. Finally, the hands of the watch are the outputs that the oscillator controls such as plasma hormone levels and the desire for sleep.

evolutionary requirement. Daily rhythmicity is reflected in the biology of most organisms even in environments devoid of timing cues. The oscillator or pacemaker recognizes local time and measures its passage, optimizing the economy of biological systems, and providing organisms with ingenious solutions to demanding problems. For example, the autotrophic cyanobacterium Synechococcus obtains its energy both from nitrogen fixation and photosynthesis: the problem is that nitrogenase is inactivated in the presence of oxygen. The solution for Synechococcus is to separate nitrogenase and photosynthesis in time, so that nitrogenase activity is restricted to night when photosynthesis (and oxygen production) are low (1).

Even though humans occupy the far end of the food chain, we also must cope with the challenge of living on a rotating world. The result is a host of rhythms that exhibit distinctive waveforms and temporal sequences, with phases that are stable and reproducible with respect to time of day. Tooth pain is lowest after lunch, proof-reading and sprint swimming are best performed in the evening, labor pains more often begin at night, and sudden cardiac death is more likely in the morning (2, 3). Modern society places impossible demands on this timekeeping system. With rapid travel across time zones, biological clocks cannot be reset immediately to destination time. The resulting symptoms of jet-lag are an irritant for travelers, a source of vulnerability for business executives and diplomats, and a serious hazard for commercial and military