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Electrophysiology of the suprachiasmatic circadian clock

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Abstract

In mammals, an internal timekeeping mechanism located in the suprachiasmatic nuclei (SCN) orchestrates a diverse array of neuroendocrine and physiological parameters to anticipate the cyclical environmental fluctuations that occur every solar day. Electrophysiological recording techniques have proved invaluable in shaping our understanding of how this endogenous clock becomes synchronized to salient environmental cues and appropriately coordinates the timing of a multitude of physiological rhythms in other areas of the brain and body. In this review we discuss the pioneering studies that have shaped our understanding of how this biological pacemaker functions, from input to output. Further, we highlight insights from new studies indicating that, more than just reflecting its oscillatory output, electrical activity within individual clock cells is a vital part of SCN clockwork itself.

Keywords: Circadian rhythms; Neuropeptides; Light; Brain slice; Extracellular recording; Patch-clamp recording; Hypothalamus; Sleep; Melatonin; SCN

Contents

Abbreviations: 5-HT, 5-hydroxy tryptamine; AHP, afterhyperpolarization; ARC, arcuate nucleus; EPSP, excitatory postsynaptic potential; GABA, gamma-aminobutyric acid; GHT, geniculohypothalamic tract; GRP, gastrin-releasing peptide; IGL, intergeniculate leaflet; IPSP, inhibitory postsynaptic potential; ERK, extracellular regulated kinase1/2; mGluR, metabotropic glutamate receptor; NMDA, *N*-methyl-D-aspartate; PACAP, pituitary adenylyl cyclase activating peptide; PKA, protein kinase A; PRC, phase response curve; PVNH, paraventricular nucleus of the hypothalamus; RHT, retinohypothalamic tract; SCN, suprachiasmatic nuclei; SP, substance P; TEA, tetraethylammonium; TTX, tetrodotoxin; VIP, vasoactive intestinal polypeptide

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1. Introduction

All living organisms, from prokaryotes to humans, contain internal time-keeping programs or biological clocks that are responsible for orchestrating the temporal architecture of an organism's physiology and behavior. The periods of these clocks which, in the absence of external input, range from less than a day to many months can be entrained by recurring exogenous signals, such that the organism's endocrine and behavioral rhythms are synchronized to salient environmental cues (Hastings, 1991).

In mammals, circadian rhythms (oscillations with periods close to 24 h) are controlled by a master clock contained in the suprachiasmatic nuclei (SCN) of the hypothalamus (Rusak and Zucker, 1979). The most compelling evidence supporting this assertion comes from studies in which circadian rhythmicity is restored to arrhythmic SCN-lesioned animals by implantation of fetal SCN material (Aguilar-Roblero et al., 1986; Lehman et al., 1987; DeCoursey and Buggy, 1989; Saitoh et al., 1990; LeSauter and Silver, 1999). In such experiments, the period of the rescued behavioral rhythm is determined by the genotype of the donor tissue, as demonstrated in studies where SCN tissue is cross-transplanted between homozygotic Tau mutant Syrian hamsters, which have circadian clocks with much shorter periods (~20 h) than the near-24 h clock of wildtype Syrian hamsters (Ralph et al., 1990). Intriguingly, restoration of rhythmic behavioral activity (but not neuroendocrine secretions) does not require direct innervation of the host brain by the graft tissue (Silver et al., 1996; Meyer-Bernstein et al., 1999).

Building on earlier work in fruit flies, remarkable progress has been made over the past 10 years in elucidating the molecular basis of the mammalian circadian clock. Thus, a number of clock genes have been discovered which, through interlocking feedback loops, regulate their transcription within individual cells so that a complete cycle occurs approximately every 24 h (for review see Dunlap, 1999; Glossop and Hardin, 2002; Reppert and Weaver, 2002; Hastings, 2003; Lowrey and Takahashi, 2004).

The molecular oscillations within cells of the circadian clock are synchronized to the environmental light–dark cycle by neural inputs to the SCN. Photic information is conveyed directly to the clock by the retinohypothalamic tract (RHT: reviewed in Ebling, 1996) and indirectly via retinally innervated cells of the intergeniculate leaflet (IGL) of the thalamus (the geniculohypothalamic tract or GHT: see Harrington, 1997). The observations that light influences expression of immediate early genes (Rea, 1989; Aronin et al., 1990; Kornhauser et al., 1990; Rusak et al., 1990; Abe et al., 1991, 1992; Colwell and Foster, 1992) and clock genes (Sun et al., 1997; Tei et al., 1997; Albrecht et al., 1997; Shearman et al., 1997; Zylka et al., 1998) in the SCN have given a preliminary insight as to how the photic information encoded by these neural inputs influences the molecular oscillations within the circadian clock. Although we know that various elements of neurotransmitter/neuromodulator signaling pathways are rhythmically expressed in the SCN (e.g. Cagampang et al., 1996a,b, 1998a,b), surprisingly little is known about how the phase-resetting information communicated by such SCN neurochemicals is conveyed to the molecular core of the clock. Further, it is still unclear how the cells in this multi-oscillatory system become synchronized, and how the SCN-clock communicates its temporal information to other areas of the brain and body. In this review, we discuss the contribution that electrophysiological studies have made to address such issues and recent insights into the role of electrical signaling in the SCN pacemaker that are beginning to fill in the gaps between the molecular clock in individual cells and circadian rhythms in the organism as a whole.

2. Historical overview

2.1. Photic input to the SCN

The study of the mammalian circadian clock with electrophysiological techniques began with the publication of a series of in vivo studies independently conducted by a number of laboratories (Lincoln et al., 1974; Nishino et al., 1976; Sawaki, 1977; Groos and Mason, 1978). These early investigations, using extracellular recording electrodes in urethane anaesthetized rodents, demonstrated that SCN neurons are spontaneously active and that the primary effect of photic stimulation of the retina (and/or electrical stimulation of the optic nerve) is to increase neuronal discharge. These observations, that light primarily activates rat (*Rattus norvegicus*) SCN neurons, were congruent with neuroanatomical findings demonstrating that RHT inputs form mostly excitatory