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Central control of peripheral circadian oscillators

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The suprachiasmatic nucleus of the hypothalamus and at least two other unidentified central pacemakers regulate the temporal structure of a circadian network that involves almost every organ in the body. Phase control is central to the efficient function of this system. Individual circadian oscillators in tissues and organs in the periphery bear adaptive phase relationships to the external light cycle, the central pacemakers and to each other. The known signals that regulate and maintain these phase relationships come from the autonomic nervous system, the pineal and adrenal glands, behavioral cycles of feeding and activity and the rhythm of body temperature. It is likely that there are many unknown signals as well. Disrupting the network can produce severe pathology.

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Introduction

It is by now clear that the circadian system of mammals is composed of multiple individual oscillators, each capable of independent motion. These are organized in a quasi-hierarchical array in which the phase relationships among the component oscillators are regulated by poorly understood signaling mechanisms producing what common sense tells us must be an adaptive temporal structure. Although such a structure was long ago predicted on the basis of sparse data and much inference, there was little direct evidence supporting it until the invention of reporter gene technology, which made it practical to assay rhythmicity in isolated, cultured cells and tissues. This technology in its several forms, along with other methods for assessing the activities of genes, has produced a flood of data leading to important general conclusions about circadian organization; among them are:

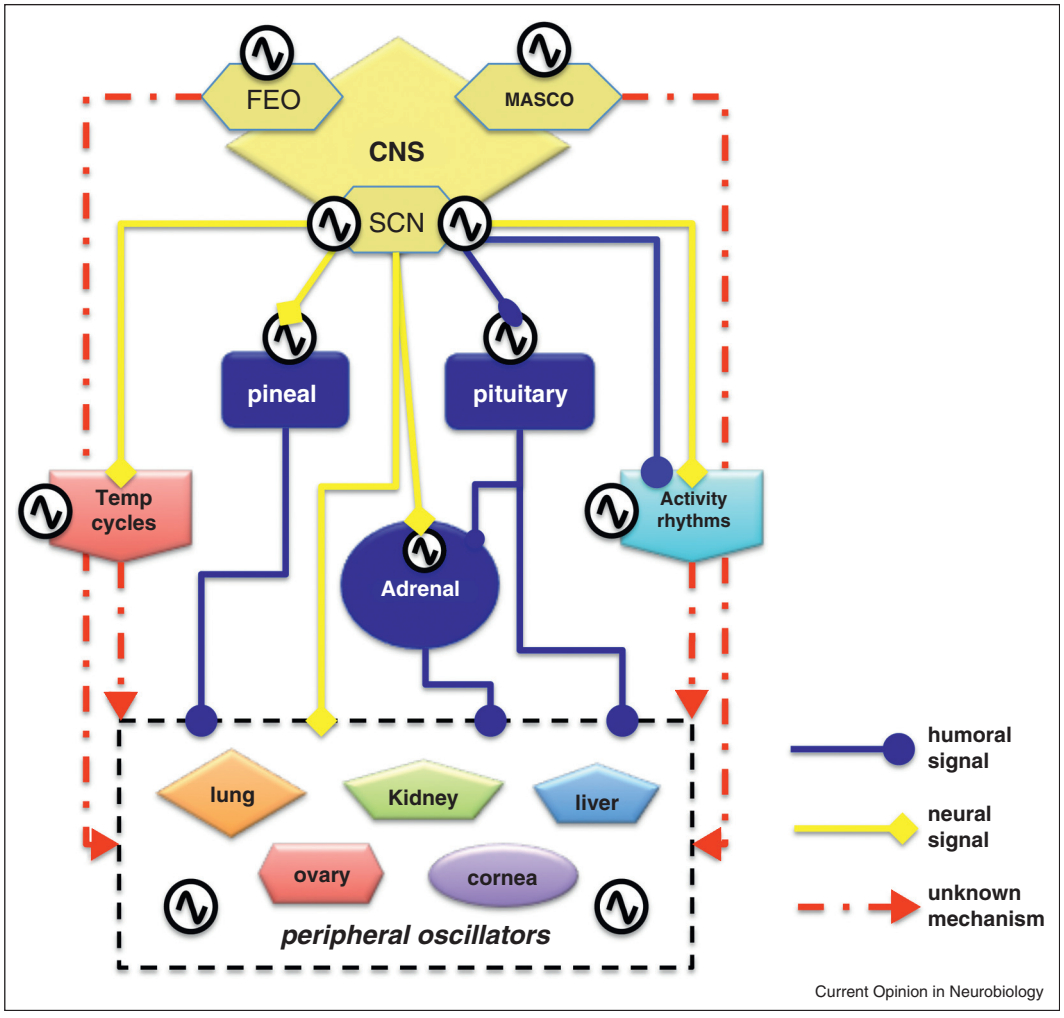
(1) Circadian rhythmicity is a cell autonomous process and most, if not all, cells are capable of generating circadian rhythms, although they may not always do so [1].
(2) Many tissues and organs in multicellular organisms are able to generate circadian rhythms independently (i.e. in the absence of rhythmic input [2,3]).
(3) In an intact organism, the phases of the independently generated rhythms of tissues and organs are regulated relative to each other and to the external environment (e.g. the light cycle perceived by the retina and affecting the SCN through the retinohypothalamic tract) [4••].
(4) There is a strong presumption that the 'normal' phase relationships among tissues and organs are adaptive. This is supported by experiments in which treatments designed to disrupt these phase relationships produce various pathologies [5–7].

The first three of these generalizations are firmly supported by experimental evidence. The degree to which the fourth is correct and the details of those adaptive phase relationships that do exist are largely unknown. They are of central importance to an understanding of the ways in which circadian organization impacts the daily lives of mammals and of the deleterious consequences of disrupting it. To understand this organism-wide temporal structure, we need to know in detail how it is regulated and maintained. We have a good start, but still a long way to go.

Central pacemakers

The discovery that the suprachiasmatic nuclei of the hypothalamus (SCN) were the dominant circadian pacemakers controlling many aspects of organism level physiology (e.g. activity, body temperature, sleep) suggested a simple hierarchical organization in which signals from the SCN directly control the phases of peripheral (and perhaps other central) oscillators [8]. There is an obvious difficulty with such a model: how does one regulate a very large number of peripheral oscillators at different phases from a single structure? One could imagine the SCN producing many different organ-specific signals or different organs responding differently to the same signal or some combination of these. Another way of organizing a temporally complex system would be to construct a network in which signals from a primary central pacemaker regulate the phases of second-order pacemakers, which in turn control subsets of peripheral oscillators, some of which may in addition be tertiary pacemakers, etc. [9]. The inevitability of feedback in such a system makes it into a network (see Figure 1). Something like

Figure 1



Pathways mediating central control of peripheral oscillators. The SCN entrains peripheral oscillators to the light–dark cycle, drives tissue level oscillations and regulates internal circadian organization. The SCN coordinates peripheral oscillators via **(1)** neural (yellow line) and **(2)** humoral (blue line) cues. Autonomic signals from the SCN entrain peripheral oscillators, including the pineal, pituitary and adrenal gland. Circulating rhythms of pineal melatonin and adrenal steroids (corticosterone and aldosterone) entrain and synchronize several peripheral oscillators. Vagal outputs driven by the SCN also affect peripheral oscillators. Through neuroendocrine pathways the SCN drives (or entrains) rhythms of pituitary hormone secretion. Pituitary hormones target peripheral oscillators directly (e.g. gonadotropins) or indirectly by regulating the secretion of adrenal steroids. The SCN regulates the timing of activity (via both humoral and neural output) and body temperature, which independently entrain and synchronize peripheral clocks. Timed meals (FEO) and methamphetamine (MASCO) entrain and synchronize peripheral oscillators, although the pathways mediating their effects are unknown (dashed red line). Although they must be numerous, potential feedback effects have been omitted because very little specific information is available.
Abbreviations: CNS: central nervous system; SCN: suprachiasmatic nucleus; FEO: food-entrainable oscillator; MASCO: methamphetamine sensitive oscillator.

this structure probably does underlie circadian temporal organization, but it must be able to accommodate the inputs of other, extra-SCN, central pacemakers that we know exist, although we know very little concrete about them.

One of these is the so-called food entrainable oscillator (FEO), the influence of which on the phases of some peripheral oscillators outweighs that of the SCN [4••,10,11,12••]. Another is the methamphetamine sensitive circadian oscillator (MASCO), which in the absence of the SCN takes over many of its functions [4••,13,14]. Neither the anatomical location nor the molecular mechanisms of these extra-SCN pacemakers are known. It is reasonable to assume that they are centrally located since they influence behavior and much of the periphery [4••,13]. All we know about their molecular mechanisms is that in both cases, their oscillation does not depend on the activity of canonical clock genes [15,16]. FEO and MASCO might be the same oscillator. Several extra-SCN regions of the brain have been identified as independent circadian oscillators, but none has been shown to act as a