Circadian rhythm regulation: a central role for the neuropeptide vasoactive intestinal polypeptide

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CIRCADIAN RHYTHM OF PHYSIOLOGY and behavior in mammals are coordinated by a pacemaker (the brain’s clock) located in the hypothalamic suprachiasmatic nucleus (SCN), which is synchronized (entrained) to the environmental light/dark cycle of 24 h. The molecular machinery driving the circadian pacemaker consists of a group of “clock” genes, which, in double autoregulatory feedback loops, interact and regulate their own transcription within the individual SCN neuron.

The pacemaker activity of the 20,000 neurons in the SCN is synchronized by a yet unknown mechanism that ensures coordinated output (14). The clock is adjusted daily by specific environmental signals (zeitgebers), which activate molecules within the SCN cells capable of transforming the incoming signal to appropriate changes in the rhythm. The most important signal is photic input via a monosynaptic neuronal pathway, the retinohypothalamic tract (RHT), which originates from a subset of retinal ganglion cells (10). The RHT costores the two neurotransmitters, pituitary adenylate cyclase activating polypeptide (PACAP) and glutamate, which influence the circadian pacemaker in a complex interplay (4).

On the basis of their neurochemical phenotype and connectivity, neurons within the rodent SCN can be separated into “shell” and “core” cells. The shell contains vasopressin (AVP) synthesizing neurons, the core region contains vasoactive intestinal polypeptide (VIP), and GABA is found in both (1). The functional significance of the various neurotransmitters of the SCN is not well understood.

Using a VIP knockout model, Colwell and colleagues (2) demonstrate in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology that VIP has fundamental functional properties for biological clock function.

The neuropeptide VIP is synthesized together with peptide histidine isoleucine (PHI) from a common precur-sor, proproVIP, and both peptides are highly expressed within the SCN (9). VIP is structurally related to PACAP, and the two peptides share receptors. The VPAC1 and VPAC2 receptors bind VIP and PACAP with almost equal affinity, whereas PAC1 receptors preferentially bind PACAP. Both the PAC1 and VPAC2 receptors are expressed in the SCN (5).

Electrophysiological and gene expression studies have suggested that VIP could be involved in light-induced resetting of the clock (11, 12). Using running wheel activity, Colwell et al. now show that VIP knockout mice have altered sensitivity to light. The knockout mice were able to sustain a stable diurnal rhythm during a 24-h light/dark cycle, but under condition of constant darkness they showed an 8 h phase advance of the predicted activity phase with less coherence and precision. Furthermore, after several days in constant darkness, nearly 25% of the VIP knockout mice examined became arrhythmic. The findings are in accordance with behavioral changes in mice carrying a null mutation in the VPAC2 receptor (Vipr2\(^{-/-}\)) (6). The Vipr2\(^{-/-}\) mice were incapable of sustaining a normal circadian rhythm of rest/activity during constant darkness but entrained to a 24-h light/dark cycle. These observations demonstrate that in both VIP and VPAC2 receptor knockout mice, running wheel behavior is controlled by the prevailing lightning conditions, a phenomenon known as masking. More important, however, are the indications that VIP signaling via the VPAC2 receptor is central to core clock functions.

What might be the mechanism behind VIP’s role in sustaining clock rhythmicity? On the basis of results from multielectrode plate recordings of individual SCN neurons, it is likely that the circadian clock consists of weakly coupled, independent oscillators (8) and that the individual circadian rhythm is synchronized by GABA (7). Colwell et al. show that VIP signaling enhances inhibitory synaptic neurotransmission in SCN neurons of unknown phenotype, which together with recent findings suggest that VIP/VPAC2 signaling influences GABA-mediated synchronization of individual oscillators (3, 13).

The study by Colwell and colleagues is the first demonstration that a neuropeptide in the SCN cells is important for maintaining stable circadian clock function. Their findings will instigate further studies on the functional implication of VIP and its receptors in the circadian system, including detailed anatomical studies of VIP receptor expression within the individual SCN cells as well as the role of VIP/VIP receptor signaling in other brain areas involved in the regulation of rhythmic behavior and physiology.

REFERENCES


