Phase Dependent Gating of the Vasoactive Intestinal Polypeptide Signaling Pathway in the Suprachiasmatic Nucleus

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Circadian rhythms are oscillations in behavior or physiology with a period near 24 hours [1]. Stimulus such as light can shift the phase of these rhythms. In mammals, the master clock coordinating circadian rhythms is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [2].

The SCN consists of 20,000 neurons whose individual circadian rhythms are dictated by the cyclic expression of clock genes [3]. The cyclic expression of the clock genes in the 20,000 neurons are usually synchronized, and vasoactive intestinal polypeptide (VIP), a peptide neurotransmitter, mediates this intercellular synchronization [4,5]. At the single cell level, the individual neurons must respond to VIP appropriately for proper synchronization. A phase response curve (PRC) plots this response as the shift in clock gene rhythmicity as a function of circadian time of treatment.

We have developed a cell-based model of the SCN which depends upon intercellular VIP signaling, entrains to light cycles and synchronizes large populations of SCN cells to each other [6]. We noted however that the PRC to VIP in the initial model lacked features that are typical of the PRC to light or glutamate [7], the signal from the retina which mediates photic entrainment. To identify key factors influencing the dead zone and the amplitude of the PRC, we used our single cell mathematical model of VIP signal transduction linked to a model describing the oscillations in clock components to generate phase response curves. This model included binding of VIP to its receptor leading to elevations in calcium and induction of the period gene, a clock component. We find that inclusion of phase dependent gating via oscillations in the receptor for VIP was sufficient to create an appropriate dead zone in the subjective day and nocturnal phase delays and advances similar to glutamate-induced shifts. We conclude that a circadian gating function at the level of the VIP receptor could be critical for mediating appropriate intercellular entrainment.

References

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