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Review Article

Alteration of circadian rhythm during epileptogenesis: implications for the suprachiasmatic nucleus circuits

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Abstract: It is important to realize that characterization of the circadian rhythm patterns of seizure occurrence can implicate in diagnosis and treatment of selected types of epilepsy. Evidence suggests a role for the suprachiasmatic nucleus (SCN) circuits in overall circadian rhythm and seizure susceptibility both in animals and humans. Thus, we conclude that SCN circuits may exert modifying effects on circadian rhythmicity and neuronal excitability during epileptogenesis. SCN circuits will be studied in our brain centre and collaborating centres to explore further the interaction between the circadian rhythm and epileptic seizures. More and thorough research is warranted to provide insight into epileptic seizures with circadian disruption comorbidities such as disorders of cardiovascular parameters and core body temperature circadian rhythms.

Keywords: Suprachiasmatic nucleus, epileptic seizures, neural crosstalk, circadian rhythm

Epilepsy and the alterations of circadian rhythm

Epilepsy is a particularly complex neurological disorder. It has been known for over 100 years that seizure occurrence relies on involvement of the diurnal, nocturnal and diffuse [1, 2]. It is now well appreciated that there exists a close link between epileptic seizures and the alterations of circadian rhythm regulation in human and animals [3-10]. Quigg et al found that postlimbic status (PLS) in patients (n=64) and mesial temporal lobe epilepsy (MTLE) in rats (n=20) occurred more often during light than dark, and between human MTLE and rat PLS had chronological similarity or similar cosinor daily distributions, suggesting that limbic seizure occurrence implicates in the circadian regulatory system [11]. By retrospectively analyzing intracranial EEG recordings, Durazzo et al determined whether seizure occurrence in partial epilepsy was under the influence of circadian rhythms and how this influence varied according to cortical brain region, and indicated that occipital and temporal lobe seizures had most likely to occur in the afternoon, whereas frontal and parietal lobe seizures had strong nocturnal preferences, suggesting that the roles of endogenous circadian rhythms in seizure occurrence vary considerably according to brain region [12]. Hofstra et al reported a prospective pilot study about timing of temporal and frontal seizures in relation to the circadian phase, and indicated that the temporal and frontal seizures occurred in a non-random fashion synchronized to a hormonal marker of the circadian timing system, suggesting that the seizure occurrence has a relation to the circadian regulatory system [13].

Epilepsy and suprachiasmatic nucleus

Many studies focused on the suprachiasmatic nucleus (SCN) neurons as the central pacemaker of biological clock [14]. It is well-established that neurons from SCN of the hypothalamus modulate and control the circadian rhythm pattern [15]. As the central pacemaker, the SCN has long been considered the primary regulator of biological circadian rhythm. The alterations of synaptic transmission in the SCN likely contribute to circadian rhythm disturbances and sleep disorder [16]. Hablitz et al reported that G protein-coupled inwardly rectifying (GIRK)

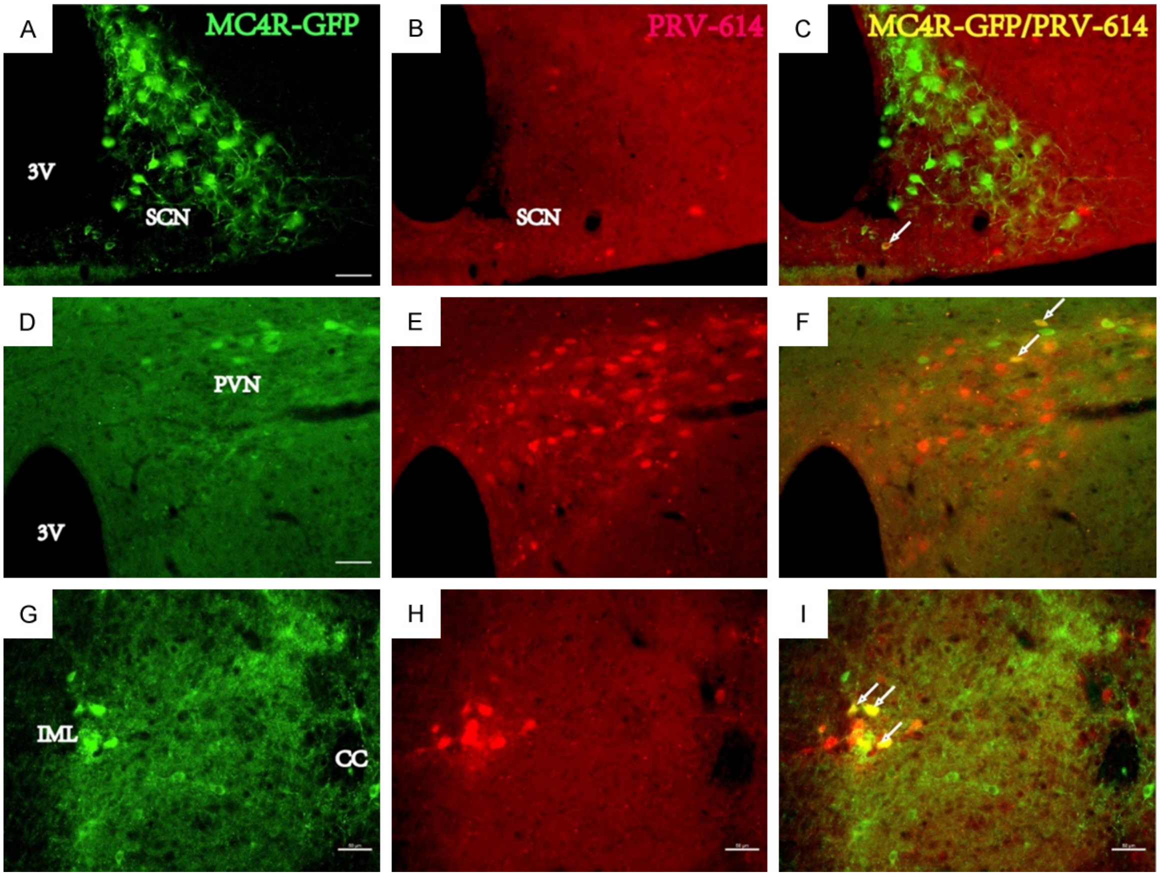

Figure 1. Transverse sections of the hypothalamus in the region of the paraventricular nucleus (PVN), suprachiasmatic nucleus (SCN), or spinal cord. Pseudorabies virus (PRV-614) was injected into the kidneys in adult male MC4R-green fluorescent protein (GFP) transgenic mice. PRV-614/MC4R-GFP dual-labeled neurons were detected in the SCN (C), PVN (F) and IML (I). (A, D, G) Showed MC4R-GFP positive cells; (B, E, H) Showed PRV-614- labeled cells; (C, F, I) Showed overlaid images of (A and B, D and E, G and H). 3V, 3rd ventricle; MC4R, melanocortin-4 receptor; CC, central autonomic nucleus; IML, intermediolateral cell column. Arrows indicated double-labeled neurons. Some drawings were taken from HB Xiang. Scale bars, 50 μm.

channel signaling within the central circadian oscillator SCN might implicate in circadian disorders with epilepsy and addiction [17, 18]. A report from Han et al demonstrated that the voltage-gated Na (+) channel 1.1 [Na(V)1.1] and its associated impairment of SCN interneuronal communication led to major deficits in the SCN function, and heterozygous loss of Na(V)1.1 channels is the underlying cause for severe myoclonic epilepsy of infancy, suggesting that the circadian deficits in the SCN may contribute to sleep disorders in severe myoclonic epilepsy of infancy patients [5].

Our research data about suprachiasmatic nucleus circuits

Neurotropic pseudorabies viruses (PRV) have become particularly important tools for transynaptic analysis of neural circuits [19-34]. There is strong evidence that the infection with PRV expressing unique reporters can be used to define more complicated circuitry [35-41]. We used PRV-614 into the kidney for exploring the suprachiasmatic nucleus circuits in adult male MC4R-green fluorescent protein (GFP) transgenic mice, and found that PRV-614/MC4R-GFP dual-labeled neurons were detected in the IML, PVN and SCN (**Figure 1**). Because there is no evidence that the parasympathetic and motor nervous system provides any innervations to the kidney, the brain neurons (SCN, PVN) were infected with PRV-614 via the sympathetic nervous system, suggesting that there may exist a direct SCN-PVN-IML circuit involving in melanocortinergic-sympathetic pathway.

Otherwise, PRV-614 injected into the left ventricular wall of the heart was specifically transported to (1) the DMV, NTS, PVN and SCN

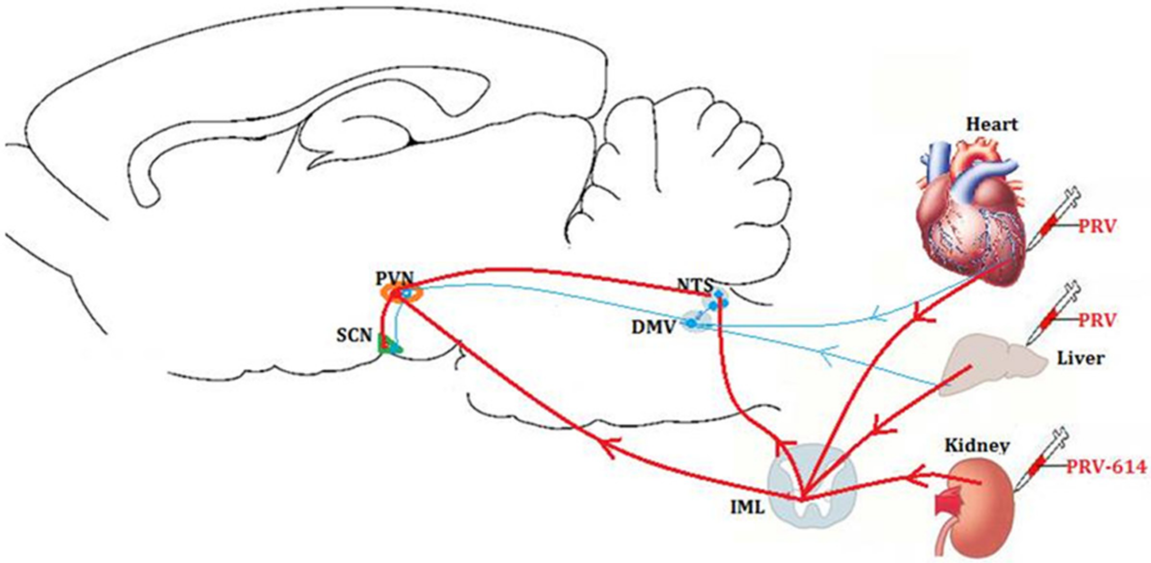

Figure 2. Summary diagram of suprachiasmatic nucleus circuits implicating in sympathetic (Red lines) or parasympathetic pathway (Blue lines). Injection of PRV-614 into the kidney, liver or heart resulted in retrograde infection of neurons in the IML of spinal cord, NTS, PVN and SCN by the sympathetic pathway. Otherwise, Injection of PRV-614 into the liver or heart resulted in retrograde infection of neurons in the DMV, PVN and SCN by the parasympathetic pathway. DMV, the dorsal motor nucleus of the vagus; IML, intermediolateral cell column; NTS, the nucleus tractus solitaries. Some drawings were taken from HB Xiang.

(**Figure 2**) by parasympathetic pathway, suggesting that there may be a link between SCN and heart by parasympathetic pathway (**Figure 2**); (2) the IML, PVN and SCN, suggesting that there may exist a direct SCN-PVN-IML circuit between SCN and heart involving in sympathetic pathway (**Figure 2**).

Suprachiasmatic nucleus circuits implicating the seizure-induced the alteration of circadian rhythm

It is important to realize that characterization of the circadian rhythm patterns of seizure occurrence can implicate in diagnosis and treatment of selected types of epilepsy [42-46]. Evidence suggests a role for SCN circuits in overall circadian rhythm (including core body temperature rhythms and circadian rhythms in cardiovascular parameters) and seizure susceptibility both in animals and humans [4, 47-49]. Thus, we conclude that SCN circuits may exert modifying effects on circadian rhythmicity and neuronal excitability during epileptogenesis. SCN circuits will be studied in our brain centre and collaborating centres to explore further the interaction between the circadian rhythm and epileptic seizures. More and thorough research is warranted to provide insight into epileptic seizures with circadian disruption comorbidities such as disorders of cardiovascular parameters and core body temperature circadian rhythms.

Disclosure of conflict of interest

None.

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