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Circadian aspects in the pathophysiology of the restless legs syndrome

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Abstract

Several pieces of evidence suggest that a dopaminergic dysfunction might play a key role in the pathophysiology of restless legs syndrome (RLS), including the therapeutic effects of dopaminergic drugs and the results of several positron emission tomography and single photon emission computed tomography studies. However, RLS symptoms display a distinct circadian pattern, with an increase of both sensorial and motor symptoms in the evening and at night. Although the latter could also be caused by homeostatic mechanisms such as a linkage to the previous amount of wakefulness, several studies performed over the last few years under semiconstant, routine conditions have suggested the existence of a 'true' circadian mechanism modulating the severity of RLS symptoms across the day–night cycle. Thus, both periodic leg movements of sleep and restlessness show a maximal severity in timely coincidence with the falling phase of the core temperature circadian cycle. The present article reviews the evidence showing circadian oscillation of dopaminergic function and postulates that the amplitude of circadian rhythm of dopaminergic function is increased in RLS, with a hypofunction at night.

Keywords: Dopamine; Periodic leg movement; Tetrahydrobiopterin; Circadian rhythm; Sleep

1. Introduction

The restless legs syndrome (RLS) is a movement disorder that affects up to 5–10% of the general population [1,2]. According to a consensus established by the International Restless Legs Study Group [3], the main clinical features of RLS are: (a) a desire to move the limbs, usually associated with dysesthesias/paresthesias in the lower extremities; (b) motor restlessness; (c) a partial, temporary relief of the former by activity; and (d) a worsening of symptoms in the evening or at night. RLS may start at any age, even during childhood [4,5], although it is usually seen in adults [6]. The clinical course usually fluctuates with time, but tends to progress with age [7,8].

RLS is a sensorimotor disorder [9]: in addition to sensorial symptoms such as dysesthesias or an urge to move the limbs, patients also experience motor symptoms such as rhythmic or semirhythmic movements of the legs called periodic leg movements during wakefulness (PLMW) when the patient attempts to remain still [10]. While sleeping, patients frequently demonstrate similar semirhythmic leg movements that have been referred to as periodic leg movements of sleep (PLMS) [11]. These are repetitive and somewhat stereotyped limb movements that usually involve the legs with extension of the great toe in combination with flexion of the ankle, knee, and, sometimes, the hip [7,12].

There is evidence to support a central role for the dopaminergic system in the pathophysiology of RLS [13]. The strongest support is based on the therapeutic effect of dopaminergic drugs [14,15] as well as on the increase of symptoms caused by dopamine receptor blockers [16]. In addition, both single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have detected decreases in type-2 dopamine (D2) receptors in the basal ganglia [17–19]. However, the reported abnormalities have been mild at best, and have even been absent in some studies [20]. In addition to the fact that sleep loss or aging might alternatively explain the findings of the SPECT and PET studies, the mechanism involved in this mild dopaminergic dysfunction also seems unclear: the SPECT data could result from a mild loss of D2 receptor density, a decrease in dopamine receptor sensitivity, or an increase in synaptic dopamine.

Cerebrospinal fluid dopamine metabolites do not differ between patients and controls [21]. Moreover, analysis of genetic association has not shown any linkage between dopaminergic transmission and RLS [22]. However, most of the previous studies have been performed in the morning or at times at which patients were not symptomatic.

Hitherto, no animal model exists for RLS. However, bilateral pharmacologic lesions in A11 dopaminergic

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neurons of the rat brain produced by microinjections of 6-hydroxydopamine caused an increase in motor activity in these animals that resembled periodic leg movements [23].

Although the involvement of the dopaminergic system in the pathophysiology of RLS seems undisputed, it does not explain by itself the fact that symptoms occur in a time-related fashion: that is, they start or are exacerbated in the evening and at night. Thus, an independent 'circadian factor' affecting or modulating dopaminergic activity has been suggested.

2. Circadian factors

As previously stated, the clinical diagnosis of RLS requires the presence of an exacerbation of symptoms at night, a factor that suggests a circadian oscillation. However, it could be argued that both motor and sensory symptoms are driven by a homeostatic rather than by a circadian mechanism. In such a case, they would be associated either to the amount of wakefulness or to some other factor indirectly related to it.

Anecdotal reports of RLS patients on shift-work or crossing several transmeridian time zones show that symptoms of RLS are related to circadian time. Shift workers experience RLS symptoms at the usual time of day when entering the night shift, and gradually phase-delay the time of onset of symptoms until coincidence with the immediate time before sleep is reached. Similarly, westward trans-meridian flights lead to a phase-delay of RLS symptoms, while eastward crossing of time zones causes an advance of phase.

Nevertheless, the main evidence for the involvement of a circadian mechanism in RLS comes from two studies that specifically addressed the question of a 'true' circadian modulation of symptoms. In these studies, the circadian rhythm of body temperature as well as the 24-h pattern of sensorial and motor symptoms were investigated in RLS patients that underwent sleep deprivation [24,25]. The monitoring conditions resembled in some aspects the methods employed in a constant routine paradigm [26]. Patients were asked to keep their activity at a low, constant level and at periodic time intervals underwent a suggested immobilization test (SIT) [27]. However, while in one of the studies the patients were asked to remain quiet and to report their subjective sensations every 15–20 min on a ten-point scale [25], in the second study the SIT was modified to allow subjects to make voluntary movements when they experienced RLS symptoms (modified SIT or mSIT) [24]. Two conclusions were reached from these studies: (1) the circadian rhythm of body temperature, a marker of circadian phase, does not differ between patients with RLS and retrospectively compared healthy subjects; and (2) the circadian oscillation of motor and sensorial symptoms can be observed even under conditions of sleep deprivation. Thus, waking leg discomfort, motor restlessness, and PLMW induced by the SIT show a peak in the early portion of the sleep period (23:00–04:00 h) and a nadir during the early portion of the wake period (09:00–14:00 h). The period of maximal frequency of PLMW coincided with the falling portion of the core temperature cycle. Similarly, PLMS during the nights of sleep peaked in the same time period. Finally, sleep deprivation exacerbates the severity of RLS symptoms, suggesting the existence of a 'homeostatic drive' as an additional factor modulating RLS symptoms.

Taken together, these studies suggest that RLS severity is determined not merely by activity, but by a circadian or a time-of-day–related factor. For a given level of decreased activity, RLS was most intense late in the circadian period (on the falling phase of the core temperature cycle whose nadir is circadian time zero) and least intense several hours later, early in the following circadian period. This rhythm was common to all aspects of RLS monitored, both subjective (patient assessed discomfort) and objective (monitoring of movement or EMG activity) and suggests the existence of a single generator for RLS.

Furthermore, the parallel course of PLMS and various subjective RLS features confirmed the close relationship between RLS and PLM. The circadian pattern of PLMS could be secondary to the phasic influence from the RLS generator and thus reflect the link between RLS and PLM. Alternatively, it could also be caused by an independent variation in the PLM generator. Interestingly, some studies have suggested that patients with RLS show the clearest pattern of early-night predominance of PLMS [28].

Although the normal circadian rhythm of temperature makes a direct involvement of the central circadian pacemaker in the pathogenesis of RLS unlikely, RLS could be linked to some biological factor that varies with the normal circadian rhythm. Proposed candidates include an altered level of sensory processing [29], which manifests itself as a decreased threshold for painful stimuli at night [30], or other biochemical factors.

3. Circadian variation of dopaminergic activity

Both animal [31,32] and human studies [33,34] suggest the existence of circadian variations in dopaminergic activity [35–38]. Human data show a distinct circadian variation, with a pattern characterized by an increase in the morning and a nadir in the late evening/night [39,40]. Furthermore, circadian variation in the dopamine system (as in other catecholamines) might influence melatonin secretion, and thus affect sleep regulation (personal observation).

Alternatively, the circadian pattern might not be generated by the dopaminergic system itself, but by other factors that indirectly modulate it. For example, tetrahydrobiopterin (TH-biopterin), a cofactor of tryptophan and the dopamine-synthesizing enzyme tyrosine hydroxylase [41], is decreased in Segawa's disease [42], another neurological disorder with a distinct circadian pattern of severity. The dopaminergic deficiencies that occur in Segawa's disease

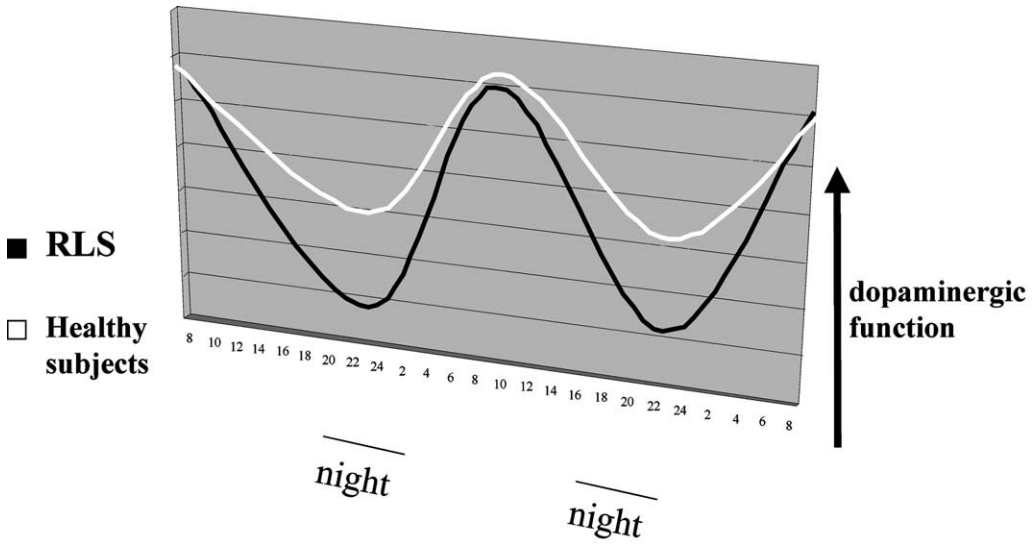

Fig. 1. Proposed model of dopaminergic function in RLS and controls. Increased circadian amplitude in the former would result in a hypofunction at night.

are caused by a deficiency in GTP-cyclohydrolase, the rate-limiting enzyme for the production of TH-biopterin [43,44]. TH-biopterin brain levels show a diurnal pattern that parallels dopamine production [32,45]. To date, cerebrospinal fluid (CSF) levels of TH-biopterins have been found to be normal in RLS when collected in the morning [21], but no similar samples have been taken while patients were symptomatic at night. It is thus possible that both RLS and Segawa's disease share a common mechanism of disease affecting the production of TH-biopterins, resulting in a distinct dopaminergic deficiency at night.

Iron, another cofactor of tyrosine-hydroxylase [41], is low in the CSF of RLS patients [46]. Serum iron shows a marked circadian variation with a low point in the evening and early night [47], a time that coincides with maximal severity of symptoms. Thus, circadian variation in serum iron parallels the circadian variation of CSF dopamine.

4. Neuroendocrine challenges

Neuroendocrine responses to dopaminergic drugs provide an additional perspective from which to investigate the function of the dopamine system. For example, the responses of prolactin (PRL) and growth hormone (GH) to various dopaminergic drugs have been used in the past to investigate the sensitivity of dopaminergic receptors to various disorders, particularly Parkinson's disease and multiple system atrophy [48–51]. Under normal circumstances, the administration of dopaminergic drugs exerts inhibitory effects on the release of PRL [52,53] and enhances the release of GH [54,55]. In a recent pilot study, nighttime administration of 200 mg of levodopa caused an increased release of GH and a reduced secretion of PRL when administered at night compared to morning administration or controls [56,57]. These preliminary results suggest the presence of hypersensitive postsynaptic dopamine receptors at night. Furthermore, a significant correlation could be seen between the PLMS-index (number of PLMS per hour of sleep) and the degree of inhibition of PRL. Taken together, the findings suggest an increase in the amplitude of the circadian variation of dopaminergic function in RLS compared to healthy controls (see Fig. 1).

In summary, circadian abnormalities represent an essential aspect of the pathophysiology of RLS. Although the function of the central circadian pacemaker does not seem to be abnormal, the severity of symptoms might be indirectly modulated by some factor undergoing circadian variation. Several substances with marked circadian fluctuation have been studied in this regard, although most investigations for both plasma and CSF biochemical abnormalities have not included an assessment of circadian function.

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