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The dopaminergic dilema: Sleep or wake? Implications in Parkinson's disease

Marcelo M.S. Lima*, Angela B. Reksidler, Maria A.B.F. Vital

Departamento de Farmacologia, Universidade Federal do Paraná, Av. Francisco H. dos Santos s/n, Jardim das Américas, Caixa Postal 19031, 81531-980 Curitiba, PR, Brazil

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Abstract The neurobiology of sleep has been quickly developed in the recent years, but the same progress of knowledge obtained for several neurotransmitters and neuropeptides were not accomplished for dopamine (DA). In fact, controversial opinions about the function of DA on sleep—wake regulation argue. The debate resides on the demonstration that DA is a substance dramatically related to sleep processes, and not associated exclusively with wakefulness events. In this sense, recent data from literature reveal that REM sleep neural pathways are triggered when D_2 dopaminergic receptors are activated on a background of reduced mesolimbic glutamatergic and serotonergic tone. Furthermore, selective lesion of the substantia nigra pars compacta (SNpc) neurons elicits a remarkable disruption of REM sleep. Additionally, the overall mean firing rate of the ventral tegmental area (VTA) neurons, present a large increase in the burst firing during REM sleep episodes. Such evidence prompts us to speculate that dopaminergic neurons present at SNpc and VTA could be consider essential for sleep regulation, in particular for triggering and maintenance of REM sleep, respectively. A clinical corroboration of this hypothesis concerned a study of motor restoration control, observed during REM sleep in Parkinson's disease (PD) patients. We propose that the paradigm of DA is being involved with wakefulness and not sleep regulation is not fully accurate. The premise stated in the current manuscript allegates that DA could present an important participation in both sleep and wake states, and each state may be accounted by differential degrees of dopaminergic modulation. The conclusion drawn from these findings is that DA has significant implications in the sleep regulation, and that particular condition has to be fully considered in respect of treatment and management of PD patients.

Introduction

The neurobiology of sleep has been quickly developed in the recent years, with remarkable neurophysiological and molecular progress of knowledge about its mechanisms.

* Corresponding author. Tel.: +55 41 3266 1720; fax: +55 41 3266 2042.
E-mail address: mmeirasantoslima@yahoo.com.br (M.M.S. Lima).

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Several neurotransmitters and neuropeptides such as noradrenalin, acetylcholine, serotonin, hypocretin (orexin) have been experimentally mapped and properly allocated in the physiological cascade of the sleep regulation [23,38,27,37,28,16,35,21,24]. However, until recently, the same progress obtained for the other neurotransmitters were not accomplished for the studies about the function of dopamine (DA) in the neurobiology of sleep. In this sense, an overview of the literature demonstrates that studies concerning a role played by DA in the sleep regulation have becoming more numerous, especially after the 1990 decade (Fig. 1). In view of that, the present scenario brings growing information about the topic and consequently controversial opinions about the function of DA on sleep are formed.

Such debate could be split in two distinct lines of thought: the first, more traditional and conservative, assumes that DA is a neurotransmitter directly involved to events that promote wakefulness and the second line, more recent, is struggling to demonstrate that DA is a hub substance dramatically related to sleep processes, in particular rapid eye movement (REM) sleep. A pioneer work originally raised this question [6] and lately, the attributed involvement of DA in the physiology of sleep has been investigated by different groups around the globe. Indeed, some of these findings demonstrated that partial DA depletion causes disturbances of REM sleep without affecting motor functions [11]. Additionally, a robust increase in the electrophysiological activity of dopaminergic neurons of the ventral tegmental area (VTA) has been identified during REM sleep [7]. Moreover, clinical evidence demonstrated a transient restoration of motor control in Parkinson's disease (PD) patients during REM sleep [8]. Additionally, dopaminergic substantia nigra pars compacta (SNpc) neurons demonstrated to be critically involved in the regulation of sleep patterns in rats, in particular REM sleep [18].

Concerning that the latest data from literature counteract the well established function of the DA on the sleep regulation, we hypothesized that the dopaminergic system, as a whole, is implicated in the physiology of sleep. In particular, we suggest that the nigrostriatal (A9) and mesolimbic (A10) pathways play a fundamental role in the trigger and maintenance of REM sleep, respectively. This hypothesis might predict numerous clinical and therapeutical implications in different dopaminergic pathologies such as schizophrenia and PD.

Activation of REM sleep by dopaminergic neurons

REM sleep is a state during unconsciousness in which the brain displays increased activation of cortical networks similar to that observed during waking, but with muscular atonia [38]. Electrophysiologically, the high-frequency brain activity, observed during the wakefulness state, is very close to the REM sleep. Such similarity could empirically suggest that the neural network involved for the generation of those theta oscillations are analogous. In fact, the high-frequency brain activity observed during waking and REM sleep is modulated via the ascending reticular activating system, which arises from the brainstem and projects to the cortex. This system is separated in two main branches: the first consists of cholinergic projections from the pedunculopontine and laterodorsal tegmental nuclei to the thalamus and the second branch projects to the basal forebrain and cortex and consists of serotonergic efferents (from the dorsal and medial raphe nuclei), noradrenergic efferents (from the locus coeruleus), histaminergic efferents (from the tuberomammillary nucleus), and dopaminergic efferents (from the ventral periaqueductal gray matter). These efferents activate neurons in the basal forebrain, which in turn modulate the projections to the cortex [34].

As of late, was proposed that REM sleep neural pathways are only activated when D_2 dopaminergic receptors are activated on a background of reduced mesolimbic

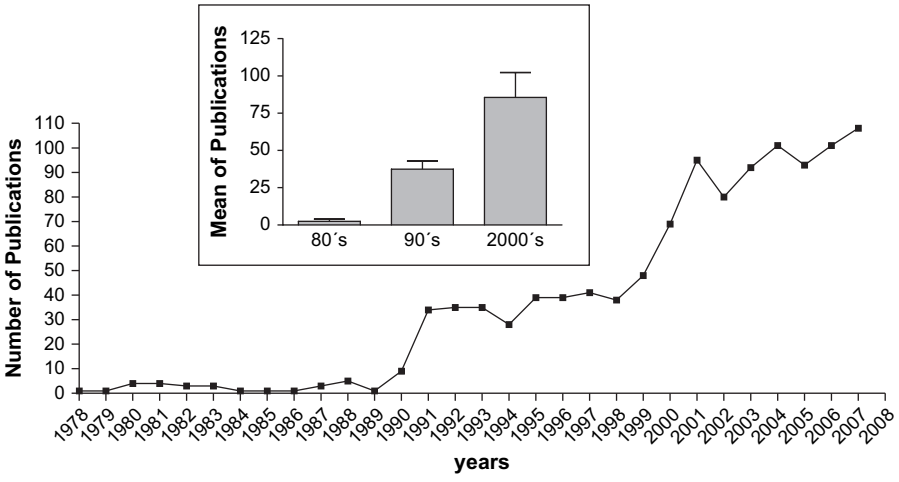

Figure 1 Number of the overall publications found in the ISI Web of Science website using the advanced search tool with the following key words: TS = sleep and dopamine. The result of the query indicated a total of 1122 papers published in the time span 1945—2008 (January). A 15.6-fold increase in the mean number of publications in the field was observed from 1980 decade to 1990 decade. 1990 decade to 2000 decade presented a 2.3-fold increment of the mean number of publications. Error bars indicate S.E.M.