Sleep Science

ORIGINAL ARTICLE

Why modeling? Mathematical models of the human sleep/wake cycle gives new insights on the pathophysiology of fatal familial insomnia (FFI)

Porque fazer modelos? Modelos matemáticos para ciclo de vigília/sono em humanos, fornecem novos insights na fisiopatologia da insônia família fatal (IFF)

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ABSTRACT

FFI, a rare prion disease, constitutes by their wake and sleep abnormalities a unique pathophysiological model of disease. Recently, a neurobiological-mathematical model of the human sleep/wake cycle (MMSWC) developed by Rempe, BestJ and Terman, reconciles circadian/homeostatic influences with new findings like the proposed sleep/wake flip-flop switch and REM-NoREM switch. We attempt now to modeling sleep abnormalities seen in FFI patients with the hypothesis that different degrees of perturbation (activation/deactivation) of circadian and homeostatic drives are related with sleep findings previously reported. We modeling our sleep data using MMSWC, where, briefly, the ventrolateral preoptic neurons (VLPO) and monoaminergic neurons (AMIN) inhibit each other and are modeled as a system of two ordinary differential equations. A similar interaction between REM-on and REM-off was also implemented. Both models were able to produce simulations that we confront with reanalyzed polysomnograms of a proven and peculiar case of FFI. IntraREM sleep fragmentation, the cyclic alternating pattern reported in atypical REM sleep and the reversal of atypical REM-NoREM presentation, seen in our case of FFI, can be simulated according the MMSWC by increasing random and Poisson perturbations on circadian and/or REM-on inputs. This was made by modifying the term I AMIN that corresponds to REM-on equations of this model. These mathematical models support the hypothesis that in FFI the extended neuronal network that regulates sleep and wakefulness could be disrupt by altered circadian/homeostatic and REM inputs.

Keywords: fatal familial, insomnia, mathematical models, sleep disorders.

RESUMO

A IFF é uma doença priônica rara constitui por alteração no estado de vigília e do sono, um modelo fisiopatológico único de doença. Recentemente, um modelo neurobiológico-matemática do ciclo vigília/sono humano (MMSWC), desenvolvido por Rempe, Best J e Terman, concilia influências circadianas/homeostático com novas descobertas, como proposta de alternância sono/vigília flip-flop e alternância REM-Norem. Tentamos agora fazer um modelo dealterações do sono observadas em pacientes FFI com a hipótese de que diferentes graus de perturbação (ativação/desativação) de unidades circadianas e homeostáticas estão relacionadas com as conclusões do sono relatadas anteriormente. Nós modelamos nossos dados de sono usando MMSWC, onde, imediatamente, os neurônios pré-óptica ventrolateral (VLPO) e neurônios monoaminergic (AMIN) inibem um ao outro e são modelados como um sistema de duas equações diferenciais ordinárias. Também foi implementada uma interação semelhante entre REM e REM-on-off. Ambos os modelos foram capazes de produzir a simulações enfrentadas ao reanalisar a polisonografia de um caso comprovado e peculiar da IFF. A fragmentação do sono intra-REM, o cíclico do padrão alternado no sono REM atípico e a reversão de apresentação atípica REM/NREM, visto em nosso caso de IFF, pode ser simulada de acordo com o MMSWC, aumentando a perturbações aleatórias de Poisson em circadiano e/ou REM-no input. Isto foi feito através da modificação do termo que AMIN correspondente a REM na equações desse modelo. Estes modelos matemáticos apoia a hipótese de que na IFF a rede neuronal prolongada que regula o sono e o estado de vigília pode ser perturbar pelas alternancias circadianas/homeostática e REM inputs.

Descritores: insônia familiar fatal, modelos matemáticos, transtornos do sono.

INTRODUCTION

FFI, a rare prion disease characterized by the Met129, Asn178 haplotype, constitutes by their wake and sleep abnormalities a unique pathophysiological model of disease[1]. It was first described by Lugaresi et al.[2], as a disease caused by a selective degeneration of the anterior and dorsal-medial thalamic nuclei. Clinically, the affected patients presents progressive insomnia with inability to produce physiological patterns of slow wave sleep (SWS), abnormal REM sleep behavior, dysautonomia, myoclonus and progressive dementia [3-7]. We have previously demonstrated, in a proven and peculiar case of FFI, the presence of reduced sleep time, typical absence of sleep spindles, atypical NREM sleep ("aNREMsleep"), fragmented atypical REM sleep ("aREMsleep") and reversal

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"aREMsleep" - "aNREMsleep" presentation[8-10]. This case, also seems to present some inherent "ultrashort ultradian periodicity" resembling a behavior that we characterized like a cyclic alternant pattern (CAP) during "aREM sleep"[11]. Recently, a neurobiological-mathematical model of the human sleep/wake cycle developed by Rempe et al.[12] based on physiological processes and interaction between neuronal cell groups reconciles circadian/homeostatic influences with new findings like the proposed sleep/wake flip-flop and REM-NoREM sleep switch[13]. Thus, this model can be applied to tests hypothesis about our findings and we attempt now to modeling sleep abnormalities seen in this case of FFI with the hypothesis that different degrees of perturbation activation/deactivation of circadian and homeostatic drives are related with sleep findings previously reported.

MATERIAL AND METHODS

We used the Mathematical Model of Sleep/Wake Cycle of Rempe et al. (MMSWC)[12] producing simulations that we confront with reanalyzed polysomnograms of our case of FFI.

Polisomnograms (PSGs) (PSGs, n = 5) were performed on 21 channels with a Nihon-Khoden polygraph. Scalp electrodes were placed according to 10-20 system in bipolar montage. During PSGs the following variables were monitored: electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), nasal and oral airflow, thoracic and abdominal effort, and pulse oximetry. Sleep-wake patterns were scored in 30 sec. epochs using standard criteria[14]. We use 5 polisomnograms, the best that we obtained, without artifacts.

"aREMsleep" (Figure 1) was characterized by briefs bursts of EEG desynchronization, low amplitude submental EMG, rapid eye movements, and brief phasic muscle twitches, and atypical NREM sleep by periods of low amplitude theta-delta activity without spindles. Measures of sleep continuity, architecture and REM sleep parameters were performed. Hypnograms were analyzed using spectral analysis of the frequency components from Fast Fourier Transform (FFT) of the raw data. "aREMsleep" periods were defined as episodes separated by at least 30 min. of clock time. "aREMsleep" - "aREMsleep" cycles were defined as the time from the end of "aREMsleep" period to the end of the next.

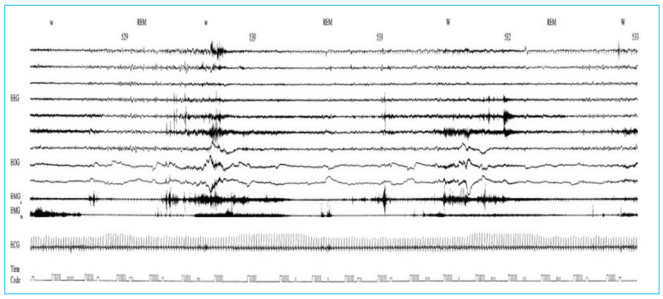

Figure 1. Polygraphic records showing the "aREMsleep" - wakefulness oscillations. EEG: electroencephalography; EOG: electrooculography; EMG: electromiography, digastric (d) and tibial (Tb); ECG: electrocardiography.

Hypnograms were also analized using spectral analysis of the frequency components from Fast Fourier Transform (FFT) of the raw data (30 seconds epochs).

All results are expressed as mean ± SEM and Student´s *t* test was used to compare differences between means. Nonparametric tests, not paired, using INSTAT-GRAPHPAD statistical software were used to determine differences and a probability less than 0.05 was considered significant.

Model of the Human Sleep/Wake Cycle of Rempe et al. (MMSWC)

This mathematical model accounts for several aspects of the human sleep/wake physiology including timing, ultradian, circadian and homeostatic dynamics based on previous "flip-flop" models[12]. A flip-flop switch could be conceptualized as a circuit containing mutually inhibitory elements, where each neuronal pool inhibits the other and disinhibits its own action and were first design by electrical engineers to produce discrete states with sharp transitions avoiding transitional states. This type of circuits are avoiding transitional states, making a wake-sleep system able to do rapid transitions and thus, behaviourly, with the capacity to respond very fast to external or internal stimuli without transitional states.

The model includes the sleep-promoting neurons in the ventrolateral preoptic region of the hypothalamus (VLPO), the wake-promoting monoaminergic cell groups (AMIN), orexin neurons (ORX), a circadian pacemaker corresponding to activity within the suprachiasmatic nucleus (SCN), and input from cortical areas (Figure 2).

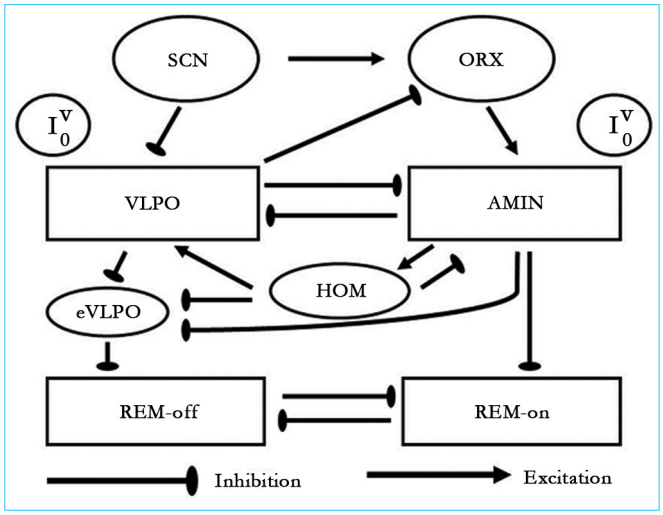

Figure 2. Block diagram of the mathematical model of the human sleep/wake (MMSWC).

The Model assumes that there is a sleep homeostat, (HOM), that increases while awake and decreases during sleep. The VLPO and AMIN are each modeled as a system of two ordinary differential equations. The authors defined eight parametric differential equations that represent Sleep/Wake and REM/NoRem cycles. We replaced the additive noise defined by

the authors and we introduced linear and non linear noise inside the circadian pacemaker as a new and effective way to obtain the best representation of the REM fragmentation in cases of FFI. These modifications do not change the dynamic and the concepts of previous model.

Rempe, Best and Terman Equations

The original Rempe, Best and Terman equations are:
For Sleep/wake cycle (Figure 3).

$$x'A = 1/dA\ (fA(xA, yA) - IVLPO + IORX + IoA - IHOM + InA)$$
$$y'A = gA\ (xA, yA)\ (7\ a,b)$$

and

$$x'V = 1/dV\ (fV(xV, yV) - IAMIN + ISCN + IoV - IHOM + InV)$$
$$y'V = gV\ (xV, yV)\ (8\ a,b)$$

where

$$f(x, y) = 3x\text{-}x3 + 2 - y$$
$$g(x, y) = e(gH(x) - y)/t(x)$$
$$IVLPO = gvlpo\ H(xV)$$
$$IAMIN = gaminH(xA)$$
$$ISCN = gscn\ C(t)$$

gvlpo, gamin and *gscn* are constants. *H* is the Heaviside function and *C(t)* represent the circadian pacemaker.

For REM/nREM cycle the corresponding equations are:

$$x'R = s'\ (fR(xR, yR) - IAMIN + INREM + IoR + InR)$$
$$y'R = s(gR\ (xR, yR))\ (9\ a,b)$$
$$x'N = s'\ (fN(xN, yN) - IeVLPO + IREM + IoN + InN)$$
$$y'N = s(gN\ (xN, yN))\ (10\ a,b)$$

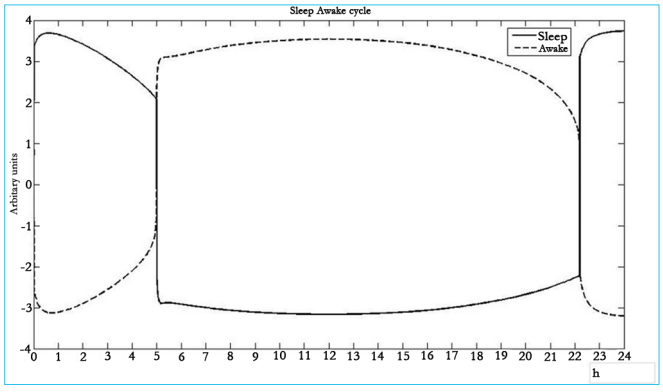

Figure 3. Modeled sleep and waking cycles.

RESULTS

Clinical Data

Briefly, reduced Total Sleep Time, "aNREM sleep" without spindles, fragmented and reduced "aREMsleep" time, sleep onset "aREMsleep" periods, reversal of aNREMsleep-aREM sleep presentation and a ultrashort ultradian "aREMsleep" rhythmicity characterized our case of FFI (Figures 4-6 and Table 1).

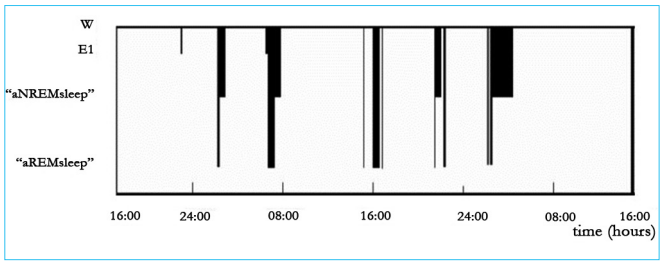

Figure 4. Hypnogram representing the occurrence of sleep during an extended PSG (48hs-dimlight conditions).

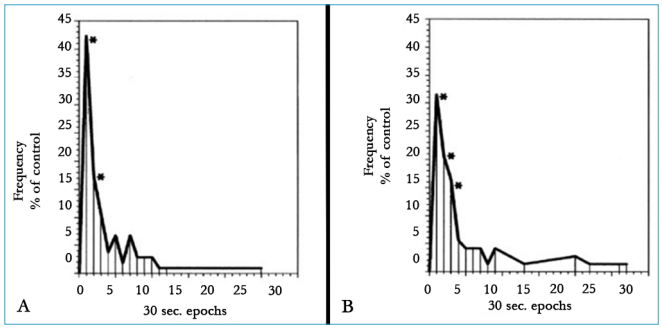

Figure 5. Periodographs showing "intra aREMsleep" (a) and "intra aREMsleep" wakefulness episodes (3b) ranging 30 to 90 seconds. * $p < 0.05$; Kruskall-Wallis NP Test; Dunn's NC Test.

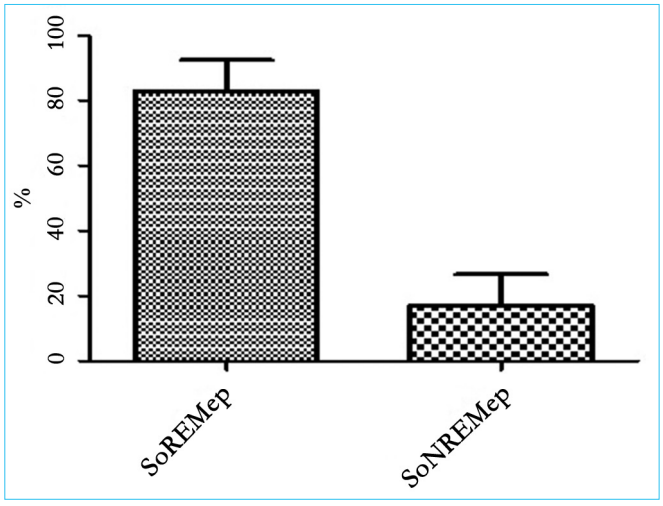

Figure 6. Frequency of sleep-onset "aREMsleep" and "aNREMsleep" episodes.

Simulations

Fragmentation effect on REM sleep introducing a noisy circadian pacemarker

The dynamics of the REM On-Off cycle were modified with noise. A noisy circadian pacemaker $C(t) = A\ (\sin\ (Q\ w\ t) + \cos\ (Q\ w\ t)) + Em(t)$ is applied (Figure 7). *Q* represents random noise, and *Em(t)* is again modeled by Macro Poisson shot noise process *N(t)*, having random pulse amplitudes and duration, which is channelled through simple exponential decay dynamics given by eq.(5).

Table 1. Polisomnograms data.

TST (%TRT)	8.3 ± 3.8
W (% TRT)	89.1 ± 3.4
Stg. 1 (% TRT)	3.2 ± 2.8
"aREMsleep"(% TRT)	5.3 ± 2.4
"aREMsleep" aw/h (#)	43.5 ± 10.3
"aREMsleep" eff (%)	37.3 ± 10.5
"aNREMsleep"(% TRT)	2.4 ± 1.6
"aNREMsleep" aw/h(#)	2.8 ± 2.8
"aNREMsleep"eff (%)	94.1 ± 7.2
"aREMsleep" P1 (min)	6.0 ± 2.8
"aREMsleep" P2 (min)	1.0 ± 0.7
"aREMsleep" P3 (min)	18.4 ± 10.1
"aREMsleep" C1(min)	98.1 ± 30.4
"aREMsleep" C2 (min)	96.1 ± 31.6

$p < 0.05$; "aREMsleep" p1-2 vs. "aREMsleep" p3.

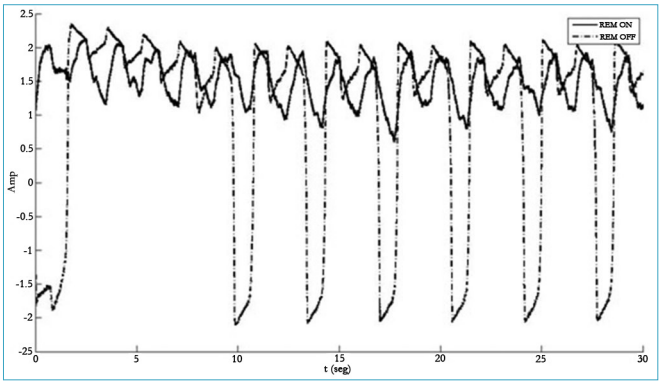

Figure 7. MMSWC simulation: REM On-Off cycle with noise.

The Macro poissonian process has the following characteristics: pulse inter arrival times exponentially distributed with mean l = 1.1, pulse amplitude uniformly distributed on {1.25, 25} and pulse durations uniformly distributed. Note that *Em* is a linear term and Q is a non-linear one. The increase in the amplitude of the noisy terms produced a scale change in the flip-flop model, fragmentating the REM/NREM and Sleep/Wake cycles.

Reversal of NREM-REM sleep presentation

Reducing iVLPO and including a noise term in each of the models of the four main cell groups does not qualitatively alter the sleep-wake behavior. However, introducing noise is an important element in making the model correctly reproduces the SoREMP data and the reversal of "aREMsleep-aNREMsleep" presentation (Figure 8). Without noise the model does not exhibit SoREMP at any circadian phase.

CONCLUSION

The oscillations observed in this case of FFI, can be compared with the oscillations obtained using the MMSWC model. In the framework of MMSWC a noisy circadian pacemarker produced

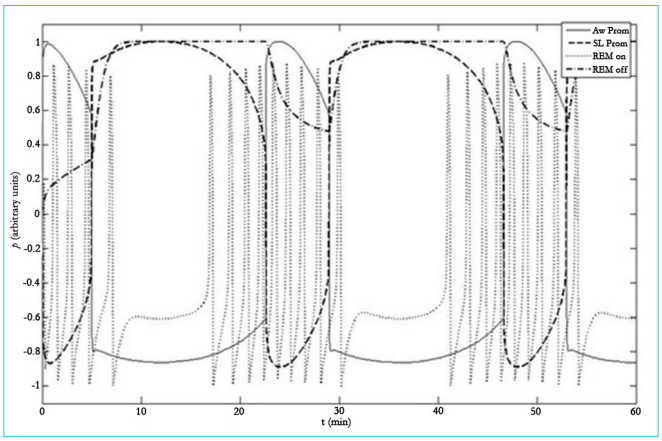

Figure 8. MMSWC simulation: Reducing iVLPO and including a noise term in each of the models of the four main cell groups.

REM sleep fragmentation. Thus, near one-minute centered cyclic alternating pattern in intra"aREMsleep" periods could be explained by circadian alterations into the dynamics of the model. This type of short-ultradian arousability, described by Terzano et al.[15,16] and also observed in this case of FFI during "aREMsleep" meaning a rol of thalamolimbic system in regulation of sleep and homeostatic-circadian functions during REM sleep. Also, the CAP sequences simulated by MMSWC and the presence of preserved ultradian rhythmicity of "aREMsleep" periods observed in our case of FFI, suggest that the oscillator regulating episodic "aREMsleep" periods continues to function during shorts periods of wakefulness[17].

The MMSWC model simulates the reversal of REM-NREM sleep presentation observed in our case of FFI. As we shown MMSWC leads to several insights and predictions concerning the human sleep/wake cycle. For example, the model predicts that during the normal sleep/wake cycle, both waking up, falling asleep and also REM dynamics are driven by the activity of VLPO. A specific role of the hypothalamus in regulating REM sleep is also suggested by the appearance of so-called sleep-onset REM periods in patients with narcolepsy and with hypothalamic lesions[18]. Thus, MMSWC support the hypothesis that in FFI the extended neuronal network that regulates sleep and wakefulness could be disrupt by thalamo-limbic disfunction disturbing circadian/homeostatic and REM inputs[19].

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