33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

A Mathematical Model to Explore the Interdependence Between the Serotonin and Orexin/Hypocretin Systems

Alok Joshi, KongFatt Wong-Lin, T. Martin McGinnity, and Girijesh Prasad

Abstract—**Among their multitude of physiological and behavioral effects, the neurochemicals serotonin (5-HT) and orexin (Ox) have been closely linked to major depressive disorders (MDD) and sleep alterations. The dorsal raphe nucleus (DRN) and the lateral hypothalamus area (LHA) are brain regions that are sources of 5-HT and Ox, and there is evidence that suggests a reciprocal interaction between them. This lends support to the hypothesis of a close relationship between MDD and sleep disorders. Based on various experimental data, and appropriate assumptions, we construct a mathematical model of the coupled DRN-LHA neural circuit. Our model relates the dynamics of four important variables that can be experimentally measured: (i) the firing rate of 5-HT-containing neurons in DRN, (ii) the firing rate of Ox-containing neurons in the LHA, (iii) 5-HT concentration level in LHA, and (iv) Ox concentration level in DRN. Simulations show that our model supports the co-existence of baseline activities and concentration levels as observed in various separate experiments. It also allows circuit-level exploration of various parameters not yet identified experimentally, e.g. the rise and decay of Ox concentration levels due to Ox neural activity, and the exact dependence of Ox neural activity on 5-HT level. Finally we have made some model predictions regarding the effects of the 5-HT antagonist on the circuit. Our model, which can be subjected to verification and refinement as new experimental data accumulates, provides unified quantitative relationships and predictions between two important connected brain regions strongly tied to MDD and sleep disorders.**

I. Introduction

The lateral hypothalamic area (LHA) of the brain is linked to the hypothalamic-pituitary-adrenal (HPA) axis, which is a major part of the neuroendocrine system that regulates a host of behaviours including sleep-wake cycle, reaction to stress, digestion, mood and emotions, and energy storage and expenditure [1], [2]. Neurons in the LHA transmit orexin (Ox) peptide which is known for its important role in sleep disorders such as narcolepsy [3].

A nearby brain region, the dorsal raphe nucleus (DRN) is a major source of the neurochemical serotonin (5-HT) that regulates mood and emotion and its abnormal activity is linked to psychiatric disorders such as major depressive disorder (MDD) [4].

Manuscript received April 15, 2011. This work was supported under the CNRT award by the Northern Ireland Department for Employment and Learning through its "Strengthening the All-Island Research Base" initiative.

Joshi et al. are with the Intelligent Systems Research Centre, University of Ulster, Magee Campus, Derry, BT48 7JL, Northern Ireland (phone: +44 28 71375320, +44 28 71375443; e-mail: joshi-a@email.ulster.ac.uk, k.wong-lin@ulster.ac.uk).

Fragmented and reduced slow wave sleep, non rapid eye movement (NREM), insomnia at all the stages of sleep and rapid eye movement (REM) anomalies are some of the most commonly observed features in MDD [5]. There is also increasing evidence from physiological studies that suggests reciprocal connections between LHA and DRN [6], [7]. However, there are only a few experimental studies of the LHA-DRN circuitry.

Most of the modeling work in this area focuses on two specific frameworks; one that combines the interaction between sleep homeostasis and the circadian system, and one based on the interaction of abstract multiple oscillators [8], [9]. However, these models do not provide details of the underlying neuronal mechanisms responsible for the pathogenesis of sleep and mood disorder. More importantly, none investigated the LHA-DRN circuit. Thus, in this paper, we use experimental data (where available) to build a mathematical model of this neural circuit and explore the dynamical relationship between 5-HT and Ox systems. Where appropriate experimental data is available we make sensible assumptions and projections. A "firing-rate" type model formalism (Figure 1A, B) is adopted to minimizes the number of free parameters in the model while allowing us to efficiently and rigorously explore the effects of these few unknown parameters on the overall circuit dynamical state.

The organization of the paper is as follows. Section II will discuss how the model is constructed. Section III will discuss the simulation results by varying the model free parameters and will demonstrate an example on simulating the effects of an antagonist on the circuit. Finally, Section IV presents the conclusions and discusses future work.

II. Model Construction

Electrophysiological recordings from Ox neurons in the LHA and 5-HT neurons in the DRN of rats and Enhanced Green Fluorescent Protein (EGFP) mice have revealed that 5-HT hyperpolarizes the Ox neurons, while Ox depolarizes the 5-HT neurons in a concentration dependent manner [10], [11], [12]. These experiments show the concentration response relationship between the applied neurotransmitter and the neuronal firing rate. Thus, we incorporate a similar approach (Figure 1A, B) for the construction of a simplified LHA-DRN circuitry.

The LHA or DRN neurons are assumed to be homogeneous and any change in the concentration level of Ox ([Ox]) can affect the population firing rate of 5-HT neurons in DRN (f_{DRN}). Similarly, any alteration in the 5-HT

concentration ([5-HT]) levels can affect the population firing rate of Ox neurons in LHA (f_{LHA}) (Figure 1B).

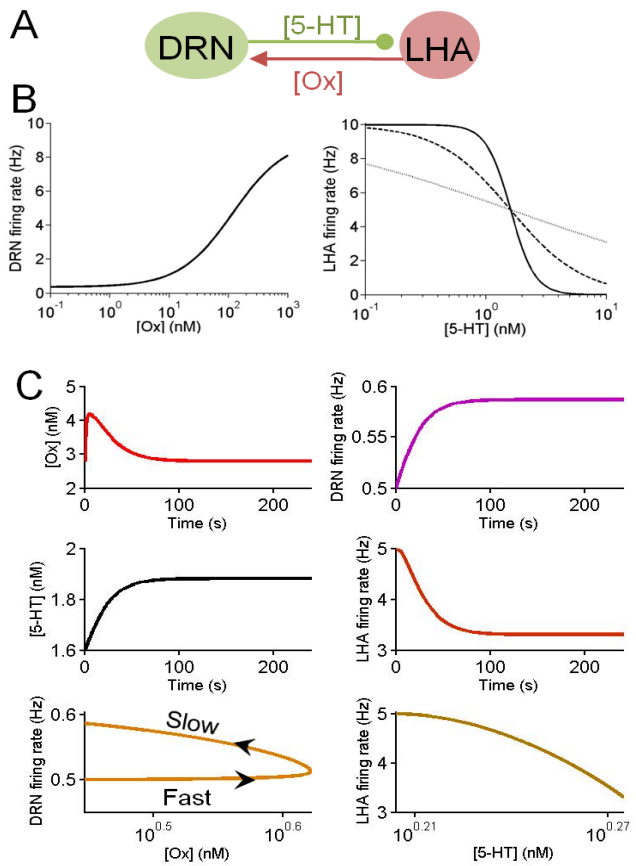

Fig. 1. A: Network model architecture. Circle (arrow): effective inhibitory (excitatory) connections [7]. B: Input-output functions for 5-HT neurons in DRN (left, cf. [11]) and Ox neurons in LHA (right) (for different slopes discussed in detail in III D, [10], [12]. C: Single-trial transient firing rates and concentration levels in the control condition. Note: Bottom two panels are transient trajectories with initial condition [Ox] = 2.8 nM, f_{DRN} = 0.5 Hz, [5-HT] =1.6 nM and f_{Ox} = 5 Hz.

Due to lack of available experimental data, we construct the model by considering the following constraints and assumptions (which can be verified in future experiments):

(i) The specific types of Ox peptides (Ox A or Ox B) are not considered in this model as the concentrations dependent change in the f_{DRN} is almost same for both types [11].
(ii) The baseline concentration level of Ox (10pg/mg~ 2.8 nM) at midbrain and DRN are the same [6].
(iii) The firing rates of 5-HT and Ox neurons are assumed to be in the range of 0-10 Hz [10], [11], [12] and [5-HT], [Ox] concentrations are in the range of 0-5 nM [6], [13] as observed in experiments.
(iv) The timescales of the effects of [5-HT] and [Ox] on neurons in LHA and DRN are estimated to be $\tau_{[Ox]} \sim 1$ min and $\tau_{[5\text{-}HT]} \sim 10$ sec, respectively. These are estimated from the effective effects of Ox and 5-HT on the firing-rate histogram time courses of the neurons [10], [14].
(v) Autoreceptors and other neuronal types are ignored.

Experimental evidence suggests that the LHA-to-DRN connection is excitatory, while the DRN-to-LHA connection is inhibitory (Figure 1A) [7]. The dynamical equations describing the population firing rates of the two pools of neurons are:

$$\tau_{[Ox]} \frac{df_{DRN}}{dt} = -f_{DRN} + F_{DRN}([Ox]) \quad (1)$$

for the LHA-DRN connection, and for the DRN-LHA connection,

$$\tau_{[5\text{-}HT]} \frac{df_{LHA}}{dt} = -f_{LHA} + F_{LHA}([5-HT]) \quad (2)$$

where $\tau_{[Ox]/[5\text{-}HT]}$ is the time constant for Ox and 5-HT effects on the f_{DRN} and f_{LHA}, respectively. F_{LHA} ([5-HT]) or F_{DRN} ([Ox]) is the input-output function between the 5-HT/Ox concentration and the firing rate of LHA/DRN neurons. The input-output function for DRN, F_{DRN} ([Ox]) is easily fitted from the available experimental data (Figure 1 B, left) [11]. However, due to unavailable data, we estimate F_{LHA} ([5-HT]) from different experimental data (Figure 1B, right) by constraining the basal values of [5-HT] ~ 1.6 nM and $f_{LHA} \sim 5$ Hz [10], [12], [13].
These estimated input-output functions are:

$$F_{DRN}([Ox]) = 0.3646 + 8.6971/(1+\exp(-(\log_{10}[Ox] - K_1)/0.4467 \quad (3)$$

$$F_{LHA}([5-HT]) = 10 - 10/(1+\exp(-(\log_{10}[5-HT] - K_2)/S \quad (4)$$

where the parameters K_1= 2.0732 and K_2= 0.2041 control the lateral shift in the input-output functions, and the third free parameter S = 0.10 controls the slope of the function in (4). These values are used as control.

To close the loop in the model circuit construction, the next important aspect is to incorporate the release-and-reuptake dynamics for [5-HT] in LHA and [Ox] in DRN. Fortunately for [5-HT], we use the established model [15] with a slight modification:

$$\frac{d[5-HT]}{dt} = [5-HT]_P f_{DRN} - V_{max}[5-HT]/(K_m + [5-HT]) \quad (5)$$

where $[5\text{-}HT]_P$ is the release per stimulus frequency artificially stimulated, and the reuptake rate (right most term) is approximated by a Michaelis-Menten equation. The maximum reuptake rate V_{max} and K_m are constants. Note that we have replaced the artificial stimulus frequency with f_{DRN} in (5) by assuming their linear proportionality, and by modifying $[5\text{-}HT]_P$ = 33.57 nM so that at basal steady state in an isolated DRN population, [5-HT] ~ 1.6 nM [13].

Similar [Ox] release-and-decay dynamics is not straightforward due to unavailable experimental data. Therefore, we assume the simplest form of equation governing such dynamics:

$$\frac{d[Ox]}{dt} = \alpha f_{LHA} - \eta[Ox] \quad (6)$$

where the free parameters decay rate (η)=0.91/s and the rise factor (α)=0.77 nM are associated with the reuptake process and linear dependence on f_{LHA}, respectively. Note that, by definition, $1/\eta < \tau_{[Ox]} \sim 1$ min, acting as a constraint.

A forward Euler numerical scheme is used with a time step of 1ms to numerically integrate (1-6). The free parameters are tuned such that the control baseline values are

close to those in experiments (section IIIA). Simulation results are discussed in the following section.

III. Simulation Results

A. Baseline firing rates and concentration levels

Under the control condition, we integrate (1-6) towards their steady state values. Figure 1C shows the transient dynamics of the four variables in a single simulation. Except for the initial fast transient of [Ox], most of the timecourse exhibit slows dynamics, most likely slaved to the slow timescale of $\tau_{[Ox]} \sim 1$ min. All the variables eventually ascend or descend towards reasonable baseline values ([Ox] =2.79 nM, f_{DRN}= 0.58 Hz, [5-HT] = 1.88 nM and f_{Ox}= 3.30 Hz). Note the interesting non-monotonic trajectory within the f_{DRN}-vs-[Ox] phase space (Figure 1C, bottom left panel), probably reflecting a brief initial adjustment period towards a steady state. This is due to the existence of some slow-fast dynamics. In the rest of the work (subsections B-C), we will focus on how the system's steady state varies with the three free parameters and plausible effects from 5-HT antagonist.

B. Decay Rate of Orexin Concentration in LHA

After identifying the control conditions, we fixed all the free parameters except the decay rate of the orexin concentration (LHA). From the simulations, we found that as the decay rate increases the steady state of Ox, 5-HT and DRN firing rate decreases and LHA firing rate increases (Figure 2A).

This relationship can be explained by the LHA-DRN feedback loop circuitry; due to the excitatory connection from LHA to DRN, the increase in the Ox decay rate decreases [Ox] in DRN and thus the firing rate of the DRN neurons decreases. This decrease in the DRN firing rate cause a decrease in the [5-HT] level at LHA, and provides a weaker inhibitory effect on LHA neurons, which eventually contribute to the increase in the firing rate of LHA neurons (Figure 2A). From these results, we can conclude that 5-HT/Ox levels are positively correlated while LHA/DRN firing rates are negatively correlated (Figure 2B).

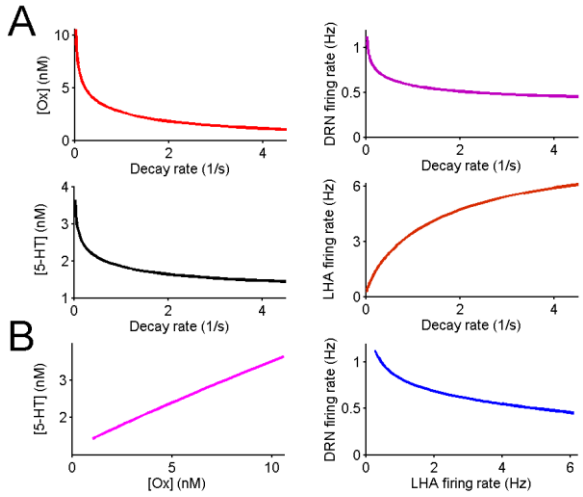

Fig. 2. Effects of decay rate of orexin concentration [Ox] on firing rates and concentration levels in the circuit. A: Steady-state values. B: Deduced relationships from A.

C. Rise Factor of Orexin Concentration in LHA

The other unknown parameter is the rise factor that signifies the per stimulus release of extracellular orexin [Ox] in the DRN. From our simulations, we found that as we increases the rise factor the concentration levels of [Ox], [5-HT] and DRN firing rate increases and LHA firing rate decreases. These trends can be explained by the LHA-DRN feedback loop circuitry in a similar way as discussed in section III B.

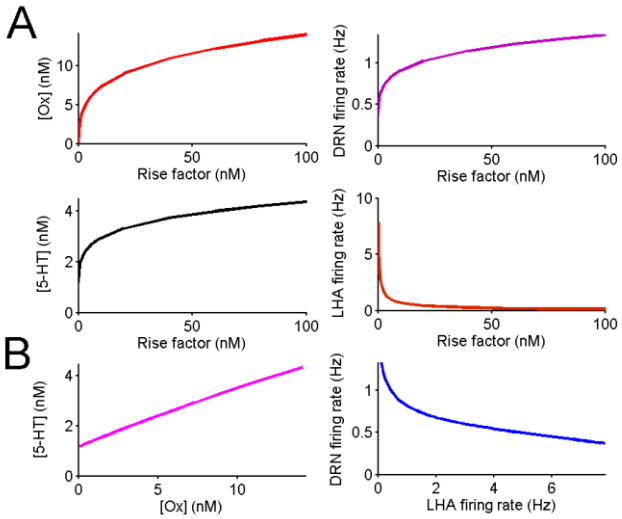

Fig. 3. Effects of rise factor of orexin concentration [Ox] on firing rates and concentration levels in the circuit. A and B: as in Fig. 2.

D. Slope of Input-output Function in LHA

The next unknown parameter of the model is the slope (S) defined for the input-output function of LHA (equation 4). The simulations results (Figure 4A) show that any positive change in slope increases the value of all the model variables (concentration of 5-HT/Ox and firing rate LHA/DRN). However, an increase in slope beyond a particular point does not significantly affect the circuit dynamics. From these results we can deduce that both the concentrations and firing rate are positively correlated (Figure 4B).

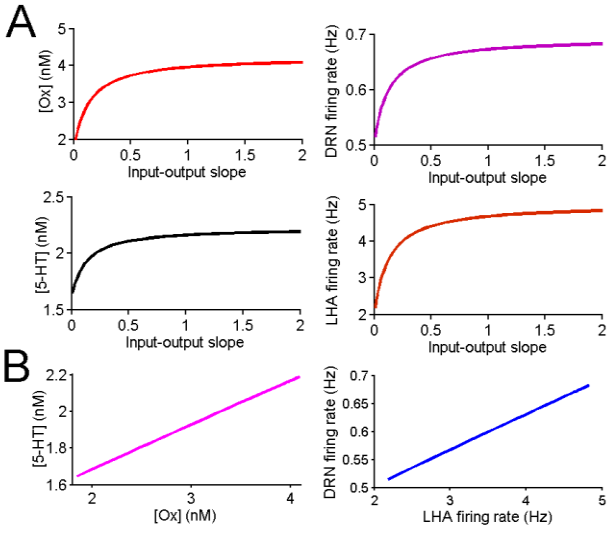

Fig. 4. Effects of slope of the LHA input-output function on the firing rates and concentration levels in the circuit. A and B: as in Fig2.

E. Effects of a Serotonin Antagonist

Having explored the free model parameters, we shall now demonstrate how we can implement and simulate the effects of an antagonist on the circuit.

According to [11], Ox antagonists laterally shift the input-output function of 5-HT neurons in DRN rightward. This is similar for 5-HT on orexin neurons in LHA. We have modeled the effective shift due to antagonist by varying the parameter K_1 and K_2 in (3, 4), assuming that the release-and-reuptake dynamics of 5-HT and Ox is unchanged.

As an example, we show in Figure 5 results for a 5-HT antagonist. Similar implementations and results hold for the 5-HT agonist, and Ox agonist/antagonist (not shown).

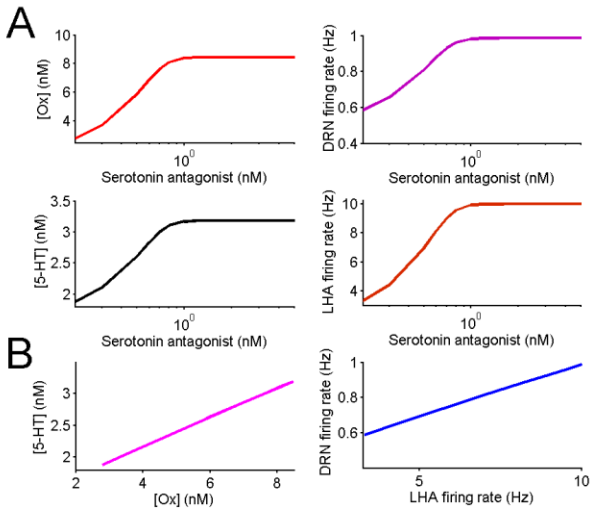

Fig. 5. Serotonin antagonist on firing rates and concentration levels in the circuit. A and B: as in Fig. 2.

IV. Discussions And Conclusions

We have built a mathematical model of a mutually coupled LHA-DRN circuit based on various known experimental data. The model is useful for evaluating quantitatively and efficiently both the transient and steady-state relationships among four important, interdependent and experimentally measurable quantities – f_{LHA}, f_{DRN}, [Ox] and [5-HT]. Although we have used the experimental data from separate experiments, our model unifies these data and supports the co-existence of the observed baseline values of these four variables.

The model is built upon the assumptions of the not yet identified release-and-decay mechanism of [Ox] and the f_{LHA}-[5-HT] relationship. We have explored three free parameters to study their effects on the circuit's steady state. These simulated data are used to correlate the system's four measurable variables (e.g. relationship between [Ox] and [5-HT], and between f_{LHA} and f_{DRN}), constituting our model's predictions. Interestingly within the range of the various parameters that we have varied, we always find [Ox] to be linearly related to [5-HT], even though the firing rate-vs-concentration functions are nonlinear. Additionally, we have implemented and studied the serotonin antagonist's effects on the circuit.

Our work constitutes a first step in modeling the LHA-DRN circuit. The model is sufficiently simple to allow refinements when more experimental data becomes available. We are planning to include more realistic features and other local neuronal types such as GABAergic interneurons. As the model matures, we will begin to incorporate it into established mathematical models of the sleep-wake cycle [8] to study the connections between sleep-wake patterns and serotonin levels, the latter being linked to depression. This approach may also allow us to quantify antidepressant drug (SSRI) effects on sleep patterns or disorder. In summary, we have established a useful mathematical model of an important brain circuit that can reveal potential insights into the relationships among depression, antidepressants, and sleep disorders.

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