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A MATHEMATICAL MODEL OF A RETINAL OSCILLATOR

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INTRODUCTION

Circadian rhythms in vertebrates (including man) have been conjectured to help control changes in sensitivity of visual systems (which must operate over some 10 orders of magnitude in the course of night and day), by anticipating the changes in light intensity which occur at dusk and dawn (Cahill and Besharse, 1995). Diurnal rhythms in melatonin and dopamine in the retina have been shown to be affected both by a circadian oscillator as well as by changes in local light levels (Cahill and Besharse, 1995). In an experiment conducted in the laboratory of one of the authors (HCH), the growth of the eyes of baby chicks in their first two weeks of life has been shown to be strongly affected by exposure to 20 hours or more of light per day (Li et al., 2000). A descriptive model of the nature of the biochemistry of retinal dynamics has been presented (Morgan and Boelen, 1996). In this work we offer a mathematical model of the retinal oscillator based on the descriptive model given in (Morgan and Boelen, 1996). Using this model we simulate the experiment described in (Li et al., 2000).

DESCRIPTIVE MODEL

In this section we describe some of the features of a simplified version of the descriptive model of retinal dynamics which has been presented in (Morgan and Boelen, 1996). See (Oyster, 1999) for a description of retinal structure and function. We focus on the interdependency of the concentrations of melatonin, dopamine and glutamate, and on their response to changes in light load.

Melatonin is produced in the photoreceptors of the retina (rods and cones). Its synthesis is high in the dark and low in the light, and is controlled by a circadian rhythm which can be phase-shifted by light (Morgan and Boelen, 1996). Dopamine is produced in amacrine cells. Its synthesis is high in the light and low in the dark. There are some reports of a limited circadian rhythm in dopamine concentrations, and we will assume that these are due to the circadian rhythm in melatonin release (Morgan and Boelen, 1996). Experiments have shown that melatonin inhibits dopamine synthesis, and that dopamine inhibits melatonin synthesis (Morgan and Boelen, 1996).

The model of (Morgan and Boelen, 1996) asserts that light causes a decrease in the neurotransmitter glutamate from the photoreceptors, leading to depolarization of ON-bipolar cells (see (Oyster, 1999)), which in turn release more glutamate to the amacrine cells, increasing dopamine release.

The functioning of the model, which is described as a dark-light switch, is dependent upon the local light level. In the dark, the photoreceptors produce melatonin which inhibits the production of dopamine. In addition, glutamate is produced by the photoreceptors, which hyperpolarizes the ON-bipolar cells, which in turn are prevented from releasing glutamate to the amacrine cells, thus maintaining a low synthesis of dopamine. By contrast, in the light the photoreceptors produce less glutamate, increasing dopamine synthesis from the amacrine cells (as described above), which inhibits the production of melatonin.

MATHEMATICAL MODEL

Our mathematical model of the descriptive model of (Morgan and Boelen, 1996) involves the following three variables:

$$m(t) = \text{melatonin concentration} \tag{1}$$

$$g(t) = \text{glutamate conc. at the amacrine cells} \tag{2}$$

$$d(t) = \text{dopamine concentration} \tag{3}$$

The differential equations governing these variables are as follows:

$$\dot{m} = -c_1\ R(t)\ (1 - f(t))\ (m - m_0) - c_2\ m\ d \tag{4}$$

$$\dot{g} = -c_3\ f(t)\ (g - g_0) - c_6\ g\ d \tag{5}$$

$$\dot{d} = -c_4\ g\ (d - d_0) - c_5\ m\ d \tag{6}$$

Here $f(t)$ is the light load:

$$f(t) = 1 \text{ for light ON}, \quad f(t) = 0 \text{ for light OFF} \tag{7}$$

and $R(t)$ is the effect of the circadian rhythm on the melatonin synthesis:

$$R(t) = A_0 + A_1 \cos(\omega t + \phi + \phi_0) \tag{8}$$

where e.g. we could take $A_0 = 1/2$ and $A_1 = -1/2$, in which case the effect of the circadian rhythm varies between 0 and 1. Here $\omega = 2\pi$ radians/day. The quantity ϕ in Eq.(8) represents the phase of the circadian oscillator and is permitted to vary in time so that the circadian clock may be reset by light loadings.

DISCUSSION

The first term in Eq.(4) represents the photoreceptor synthesis of melatonin. It is zero when the light is on, i.e. when $f(t) = 1$, and it is modulated by the circadian rhythm $R(t)$. In the absence of light, of circadian rhythm and of inhibition by dopamine (given by the last term in Eq.(4)), m approaches the equilibrium value m_0.

The second term in Eq.(4) represents the inhibition of dopamine on melatonin synthesis and is modeled by a simple chemical kinetic term. A more sophisticated treatment of this term and the comparable terms in Eqs.(5),(6), would involve replacement by Michaelis-Menten kinetics (see e.g. (Rubinow, 1975)). For Eq.(4) this would be given by:

$$-\frac{c_2\ m\ d}{1\ +\ b_1\ m\ +\ b_2\ d\ +\ b_3\ m\ d} \tag{9}$$

The first term in Eq.(5) states that when the light is on, the concentration of glutamate at the amacrine cells approaches the equilibrium $g = g_0$, at least in the absence of the second term. The latter represents the decrease in the concentration of glutamate due to interaction with dopamine.

The first term in Eq.(6) states that in the presence of glutamate, dopamine approaches the equilibrium $d = d_0$, at least in the absence of the second term. The latter represents the inhibition of dopamine synthesis by melatonin.

RESETTING THE BIOLOGICAL CLOCK

It remains to describe the modeling of the resetting of the biological clock by light loadings. We suppose that the phase ϕ in Eq.(8) is constant between resets, and that resetting occurs each time the light is switched from ON ($f = 1$) to OFF ($f = 0$). Experiments have shown that it takes several days for the circadian rhythm to reset under periodic light loading. Thus we wish to be able to tune the resetting process with a parameter (α) which controls how rapidly resetting occurs. Let $\{t_n\}$ be the set of times at which the light $f(t)$ jumps from 1 to 0. Then we set:

$$\phi_{n+1} = \phi_n + \alpha \sin(\phi_n + \omega t_n) \tag{10}$$

It can be shown that in the case of a diurnal light loading which switches from light to dark once per day, Eq.(10) gives that $\phi_n \to -\omega t_0$, where t_0 is the daily time of the jump from ON to OFF. Substitution of this result into the expression for $R(t)$ in Eq.(8) shows that the rhythm resets to the light loading.

SIMULATION OF EXPERIMENT

We have used the model described in this work to simulate the experiment in ((Li et al., 2000)). For a given light load, we are able to predict the melatonin levels as a function of time, given the many parameters of the model. In particular we can compare the effects of a single periodic block of 4 hours of darkness, with a daily light load of 4 one-hour blocks of darkness, the latter timed either in a regular or random fashion. It was found in ((Li et al., 2000)) that these different light loads produced different amounts of corneal flattening in chicks.

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