Computers in Biology and Medicine 63 (2009) 1058 – 1062

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Modeling schizophrenic-like neuronal patterns using nonlinear delayed differential equations

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ARTICLE INFO

Article history:
Received 23 October 2008
Accepted 25 August 2009

Keywords:
Hyperdopaminergic
Glutamate
Pyramidal neurons
Cortical–striatal–thalamic loop

ABSTRACT

We examined the simultaneous effect of altered dopamine and glutamate level on pyramidal cells using a mathematical model. The simulation results suggest that increased dopamine brings about irregular and aperiodic activity, interpreted as schizophrenic state. Hypoglutamatergic conditions have the same effect on the membrane potential of pyramidal cells. Increased glutamate level was able to neutralize the effects of the hyperdopamine state and normal periodic bursting behavior appeared. We suggest that glutamate receptor activation may have therapeutic results in schizophrenic patients. Surely, this hypothesis must be evaluated in the light of experimental studies on animal models or clinical trials.

1. Introduction

Schizophrenia is accompanied by many disorders in higher-order brain functions including disruption of information processing and sensory perception, abnormal mood and affect, deep cognitive impairments and movement abnormalities [1].

Most current researches on the etiology of schizophrenia focus on the brain micro-structural abnormalities. A variety of deficits, from the cellular to cognitive performance level, have been observed in schizophrenia. However, none of these abnormalities are accepted as a clear etiology of schizophrenia.

The "Dopamine hypothesis" is one of the main biochemical theories on schizophrenia, claiming that the disorder results from dopamine (DA) over-activity in the brain.

Glutamate, the primary transmitter of pyramidal neurons, may also have a role in schizophrenia. The interaction of glutamate and DA in the striatum, through changing the activity of thalamus, has been proposed to underlie the defective sensory filtering of schizophrenia. It seems that a combination of hypoglutamatergic and hyperdopaminergic conditions may result in reduced activation of the striatal complex and induce psychosis [2].

Curative treatment may not be possible, until the etiology of schizophrenia is well-understood. Current palliative treatments of schizophrenia include both pharmacological and psychosocial issues. More researches on interventions aimed at the improvement of cognitive deficits and functional status is needed.

Based on symptoms and treatment outcomes, a number of subclassifications have been proposed for this disease. Subtypes based on symptom profiles include predominantly positive versus predominantly negative, as well as subtypes specified by the DSM-IV and ICD-10, including simple, hebephrenic, catatonic, paranoid, disorganized, undifferentiated, and residual [3].

On the other hand, modeling the biological systems is a proper route for evaluating complex brain behaviors which can be used to mimic different mental diseases. Modeling the biological systems has at least three advantages: analyzing the system, predicting its behavior in different conditions, and finally controlling it.

Because of the complexity and heterogeneity of schizophrenia, few models have been proposed for this disease [4]. Most of the proposed models are descriptive rather than mathematical.

Narayanan attempted to model the cortical–striatal–thalamic loop and proposed that his model produces a better match than other models to the data of schizophrenic patients on the standard cognitive test, the Wisconsin card sorting task (WCST). In this test, subjects sort a deck of 128 cards according to some specific criteria. Cards vary by color, form, and number (each having four values). The subject places each of the 128 stimulus cards in front of a target card and gets a response from the experimenter. Once the subject has made 10 correct responses a category is achieved and the rule (sort according to one of the features) is arbitrarily changed. The test is completed when six categories are achieved or all 128 cards are used [5].

One of the most important models is presented by An der Heiden [6]. In this model, the effect of different levels of dopamine concentration on firing patterns of pyramidal cells is studied and it is shown that changing the dopamine level leads to the bifurcation of the

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doi:10.1016/j.compbiomed.2009.08.008

system between health and disease. He has not studied the effect of glutamate. Since the glutamate system is emerging as an important neurotransmitter in schizophrenia [1], we present a mathematical model in this study to analyze the simultaneous role of altering the concentrations of both dopamine and glutamate neurotransmitters on producing psychosis.

2. Model description

Here, we use the mathematical model developed by [7]. Although their model is not directly on the cortical–striatal–thalamic loop, the similarity between some parts of their circuit and our desired loop helps us to bring about an effective modeling approach. Their model is a recurrent inhibitory circuit in the hippocampus. This mode considers three neuronal populations: the *presynaptic fibers*, which excite the *postsynaptic cells* and the *inhibitory interneurons.* The interneurons are activated by axon collaterals from the postsynaptic cells and, in turn, return an inhibitory input to the postsynaptic cells.

The postsynaptic cell has an input given by $E(t)-I(t)$, where $E(t)$ (in millivolts) is the excitatory postsynaptic potential (EPSP) due to activity in the presynaptic cell, and $I(t)$ (in millivolts) is the inhibitory postsynaptic potential (IPSP) resulting from the activity in the inhibitory interneuron. The output of the postsynaptic neuron is the action potentials occurring at a frequency of $F(t)$, (in Hertz). Assume that this postsynaptic cell output is given by

$$F(t)=x\vartheta(E(t)-I(t)-\theta) \tag{1}$$

where

$$\vartheta(y)=\begin{cases}0, & y\le 0\\ y, & y\ge 0\end{cases}$$

In Eq. (1), the constant x (Hz/mV) is the slope of the "firing frequency versus postsynaptic cell input" curve, and θ is the threshold (in mV). The postsynaptic cell activity stimulates the inhibitory interneurons, producing action potentials which arrive at the synaptic terminals with a frequency $\tilde{F}(t)$ and leads to the generation of the IPSP, $I(t)$. Because of the resistive–capacitive properties of the postsynaptic cell membrane, this inhibitory potential decays at a characteristic rate of γ ($\mathrm{m\,s^{-1}}$). The dynamics of the IPSP are

$$\frac{dI}{dt}=-\gamma I+\eta\tilde{F} \tag{2}$$

η (mV) is a time-dependent inhibitory interaction coefficient given by

$$\eta(t)=TV_mG(\tilde{F}(t)) \tag{3}$$

where T is the average number of inhibitory postsynaptic receptors per cell, V_m (mV) is the inhibitory potential resulting from the activation of one receptor, and $G(\tilde{F})$ is the fraction of inhibitory receptors available for activation by the neurotransmitter.

To determine $G(\tilde{F})$, assume that the receptor–transmitter interaction is governed by the reaction

$$M+nC\leftrightarrow L$$

where n is the number of molecules of transmitter (C) required to activate one receptor, L is the number of active receptors of total receptor population T, and M is the number of inactive receptors.

Therefore, in this chemical reaction the fraction of receptors available for activation is

$$\frac{K}{K+[C]^n}$$

where K is the equilibrium constant for the transmitter–receptor reaction, and $[C]$ is the neurotransmitter concentration.

Taking the assumption that the pool of inhibitory transmitter is sufficiently large not to be depleted by interneuronal activity, the relation between released transmitter levels and interneuron firing frequency is

$$[C]=m\tilde{F}$$

where m is a constant. Thus, the function $G(\tilde{F})$ is given by

$$G(\tilde{F})=\frac{K}{K+(m\tilde{F})^n} \tag{4}$$

To relate the action potential rate at the interneuron axon terminal ($\tilde{F}$) to the frequency of action potential in the postsynaptic cell (F), we assumed that the activity in the postsynaptic cell at a frequency $F(t)$ requires a finite time τ to be translated into activity at the axon terminal of the inhibitory interneuron. Thus we take

$$\tilde{F}(t)=\alpha F(t-\tau) \tag{5}$$

where α is the reciprocal of the number of action potentials in the postsynaptic cell required to elicit one interneuronal action potential. Eqs. (1)–(5) may be combined to give

$$\frac{dI(t)}{dt}=-\gamma I(t)+\alpha TV_mF(t-\tau)\frac{K}{K+(m\alpha F(t-\tau))^n} \tag{6}$$

and

$$F(t)=x\vartheta(E(t)-I(t)-\theta) \tag{7}$$

Eqs. (6) and (7), in conjunction with an initial condition $I(t)=I_0(t)-\tau\le t\le 0$, and a specific amount of $E(t)$, produce a complete description of the simplified recurrent inhibitory feedback neuronal network. Rewriting the equations in dimensionless form, the following notation is introduced:

$$\bar{t}=t/\tau,\quad \psi^n=K\Big(\frac{\tau}{m\alpha}\Big)^n$$

$$e(\bar{t})=E(t)/\theta,\quad \Gamma=\gamma\tau$$

$$i(\bar{t})=I(t)/\theta,\quad \beta=\alpha T\psi V_m/\theta$$

$$f(\bar{t})=\tau F(t)/\psi,\quad H=\tau x\theta/\psi \tag{8}$$

Using (8), Eqs. (6) and (7) may be written as

$$\frac{di(\bar{t})}{d\bar{t}}=-\Gamma i(\bar{t})+\beta g(f(\bar{t}-1)) \tag{9}$$

$$f(\bar{t})=H\vartheta(e(\bar{t})-i(\bar{t})-1) \tag{10}$$

In which

$$g(f)=\frac{f}{1+f^n} \tag{11}$$

2.1. Physiological plausibility of the model

In this section, we will match the abovementioned model to a recurrent inhibitory circuit in the cortical–striatal–thalamic loop which is involved in schizophrenia.

A direct and an indirect loop project to the thalamus. Most corticostriatal projections have contacts with striatal GABA neurons which in turn project to the thalamus. These convergent pathways have two or three inhibitory GABAergic interneurons before giving feedback to cortex via thalamic glutamatergic neurons (Fig. 1a) [2].

The direct pathway in the cortico–striato–thalamocortical loop has two GABAergic interneurons that disinhibit the thalamus. In combination with the D1 recoptor-coupled dopamine pathways projecting from the substantia nigra, this pathway activates the