Journal of Theoretical Biology 254 (2008) 361–367

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Huntington's disease: Modeling the gait disorder and proposing novel treatments

Masood Banaie [a], Yashar Sarbaz [b], Shahriar Gharibzadeh [b,*], Farzad Towhidkhah [c]

[a] Department of Biomedical Engineering, Faculty of Technical Sciences, Shahed University, Iran
[b] Neuromuscular Systems Laboratory, Bioelectrics, Biomedical Engineering Faculty, Amirkabir University of Technology, Tehran 15875-4413, Iran
[c] Biological Systems Modeling Laboratory, Biomedical Engineering Faculty, Amirkabir University of Technology, Iran

ARTICLE INFO

Article history:
Received 10 January 2008
Received in revised form
18 May 2008
Accepted 19 May 2008
Available online 28 May 2008

Keywords:
Basal Ganglia (BG)
Diazepam
Glutamate
GABA (gamma amino butyric acid)

ABSTRACT

Huntington's disease is a movement disorder originated from malfunctioning of Basal Ganglia (BG). There are some models for this disease, most of them being conceptual. So, it seems that considering all physiological information and structural specifications to develop a holistic model is needed. We introduce a computational model based on experimental and physiological findings. Parts of the brain known to be involved in Huntington's disease are all considered in our model and most features of the movement disorders have been appeared in the model. This mathematical model has considered the involved parts of the brain in a fairly accurate way, explaining the behavior and mechanism of the disease according to the physiological information. Our model has several advantages. It is able to simulate the normal and Huntington's disease stride time intervals. It shows how the present treatment, i.e. diazepam, is able to ameliorate the gait disorder. In this research we assessed the effects of changing some neurotransmitter levels in order to propose new treatments. Although we showed that gamma amino butyric acid (GABA) blockers reduce Huntington's disease movement disorder, but we discussed that it is unfair to use this route for treatment. We evaluated our model response to increment of GABA, alone and observed that the gait disorder was strengthened. Our novel idea in this regard is resuscitation of BG loop in order to maintain its major physiological functions, and at the same time raising the threshold in order to weaken the internal disturbances. Our last idea about BG treatment is to decrease glutamate. Our model was able to show the effectiveness of this treatment on Huntington's disease disturbances. We propose that experimental studies should be designed in which these two novel methods of treatment will be evaluated. This validation would implement a milestone in treatment of such a debilitating disease at Huntington.

1. Introduction

Huntington's disease (HD) is one of the movement disorders originated from malfunctioning of Basal Ganglia (BG). The BG is a collection of subcortical nuclei that are involved in the control of movement. Degeneration of specific neurons in the striatum (input part of BG) results in the movement disorder. The symptoms appear in almost all movements of the patient suffering from HD (Guyton and Hall, 2001; Kandel et al., 2000). HD exhibits vast movement symptoms especially hyperkinesia, which includes chorea, ballism, and athetosis.

Chorea involves very similar excessive, involuntary movements, similar to those of ballism, but less abrupt and wild. Ballism, on the other hand, involves rapid flailing movements. Finally, athetosis is slow writhing movements of the fingers, hands, and sometimes toes. The symptoms significantly appear in limb movements. The gait records are one of the main resources for studying these disorders. Time series of gait is different among HD and other movement disease like Parkinson's disease (Rothwell, 1994).

Because of the complexity of BG architecture, there are few computational researches about HD. Nowadays, researchers study more about HD, because of its vast range of movement disorders. There are small ranges of successful studies about HD treatment. One of the treatments is using Diazepam (Kennedy et al., 2005). In fact, this drug decreases the role of BG in controlling the movements. Because of omitting the modulatory effect of BG, HD symptoms are diminished with this drug, but some other problems arise (http://www.emedicine.com).

There are some models for HD, most of them being conceptual (Glass et al., 2000). There are rare computational models available (Banae and Sarbaz, 2005; Sarbaz et al., 2007). There are similar

* Corresponding author. Tel.: +98 21 6454 2369; fax: +98 21 6649 5655.
E-mail address: gharibzadeh@aut.ac.ir (S. Gharibzadeh).

0022-5193/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2008.05.023

problems for other BG diseases like Parkinson's disease (Haeri et al., 2005). In addition, a few studies focus on assessment of symptoms only. Some of them present a mathematical analysis for them (Hausdorff et al., 1997). However, these researches have introduced no relation between results of their studies and physiological findings. So, it seems that considering all physiological information and structural specifications to develop a holistic model is needed for better studying and analyzing HD. It should be noted that most of the previous researches have assessed the response of the system but they had few comments on controlling the movement disorders of the disease.

We want to introduce a computational model, based on experimental (clinical) and physiological findings. Parts of the brain known to be involved in HD are all considered in our model. Therefore, most features of the movement disorders have been appeared in the model. This mathematical model has considered the involved parts of the brain in a fairly accurate way, explaining the behavior and mechanism of the disease according to the physiological information.

2. Physiological background

We have tried to use most of the available physiological information to model HD in a correct way. Available findings about BG include both information about inner parts of each BG block and the relations between them. Regarding the relation between the blocks, we know the number of blocks and their inputs and outputs. In addition, interactions between blocks such as their inhibitory and excitatory effects are known. The neurotransmitters connecting the different blocks are identified. The summary of this information is represented in Fig. 1.

About inner parts of each block, we have no significant information. To introduce a computational model, we need to have a glance on inner parts of each block. All we found in scientific texts is that each block contains many numbers of neurons. Therefore, the function or dynamics of each block is not known. Then, we have modeled each block based on neuronal properties. All characteristics of a neuron such as membrane behaviors, threshold, firing rate, etc. were considered. We used a first-order transfer function as the membrane behavior, a relay unit as the threshold, and a wrap to zero instead of firing rate. A delay is also used for each neuron.

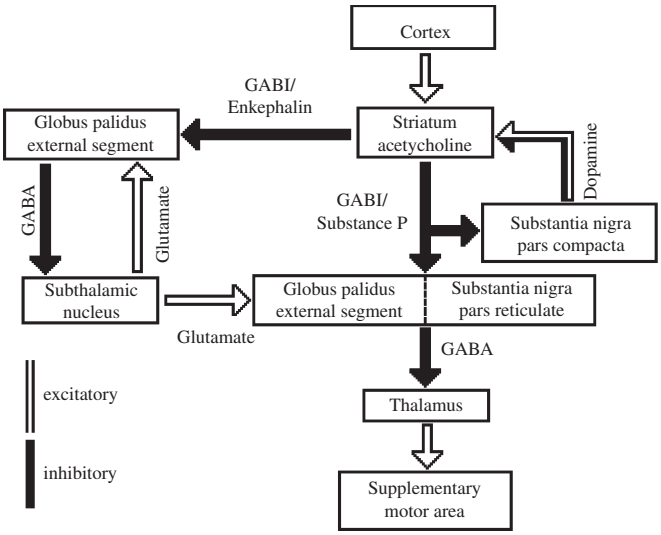

Fig. 1. A schematic diagram of the different neurotransmitters used in the connections of the Basal Ganglia (Kandel et al., 2000).

Additionally, we have some information about the connection weight variations in patients, compared to healthy persons. These differences are presented completely in Fig. 2.

We have used clinical records of gait disturbances to validate our model. The database is records of stride intervals during walking. It contains normal persons as control cases and HD patients. It was obtained from Physionet database (http://www.physionet.org).

3. Mathematical model

As discussed above, the structure of model was designed as the schematic diagram shown in Fig. 1. The number of inputs and outputs of each block is considered. The kinds of interactions between blocks are designated; i.e. if a connection (neurotransmitter) is an excitatory one, we have modeled it as a positive gain, else (an inhibitory connection), we have used a negative gain.

The input of BG from cortex was considered as a constant value, because the movement disorders of HD are caused by BG and its internal parts. Hence, the input from cortex in both healthy and disease states would be similar. The output of our model is denoted as the gait disorder. Hence, it is considered that the gait problem is in BG output. Then, muscle dynamic, skeletal system and other parts of neural system as spinal cord were ignored; because these parts are similar in both controls and patients (Coté and Crutcher, 1991).

There were limited studies available about inner relations and functions of each BG block. Therefore, we have considered each block as a set of too many neurons working together. Then, we proposed a single neuron model in a manner that it can satisfy all characteristics of a real neuron. Each neuron includes a membrane that receives signal from extracellular space and passes it to intracellular region with a delay. The membrane behavior is similar to the performance of a circuit that includes a resistance and a capacitor (Kandel et al., 2000). This circuit's transfer function is a first-order one. Hence, we have used a first-order transfer function to simulate membrane properties.

In addition, each neuron has an activation threshold, which is the minimum stimulation needed to activate the neuron. Therefore, we have considered a nonlinear function (on/off relay with a shift). On the other hand, after producing an action potential, the neuron quickly returns to its rest state. We designated this behavior using a "wrap to zero" block. After passing from threshold voltage, we see a positive feedback behavior, because membrane sodium channels open; then the neuron would be depolarized and this depolarization opens new sodium channels and this behavior continues. In the model, we use a positive feedback in each block after threshold to simulate this behavior. In each block, we have a time delay for transmitting signals. This delay is considered in our model. It is notable that the values of the model parameters are selected according to the final response of the system (gait disorder). The complete schema of our model is shown in Fig. 3.

The notations for nomenclature of the gains (g) on block connections are as follows: each connection name that ends to "l" is a connection which will be lost in HD state; each name that ends to "i" is a connection weight that increases and each name that ends to "d" is one which decreases in HD. All gains ending to "t" are designated to assess the HD treatment in the model and to research on the new treatments.

In the HD state, in addition to the changes discussed above, one of neurotransmitters in BG, glutamate, becomes toxic; i.e., the