Pathophysiology of freezing of gait and some possible treatments for it

Yashar Sarbaz, Shahriar Gharibzadeh *, Farzad Towhidkhah
Neuromuscular Systems Laboratory, Biomedical Engineering Faculty, Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran

A R T I C L E   I N F O
Article history:
Received 13 August 2011
Accepted 27 October 2011

A B S T R A C T
Freezing of gait (FOG) is a disabling symptom of Parkinson’s disease (PD). In this study, we used the model of PD gait behavior for comparing normal and PD persons in order to simulate FOG and find its pathophysiology and probable treatments. We observed in the adapted model that the dopaminergic weights were reduced and the amount of dopaminergic bias was increased. These findings show that the aggravation of the disease and severe resistance of neurons to dopamine agonists may be the main cause of the FOG. Based on our model three therapeutic strategies may be proposed: decreasing the cortex signal to basal ganglia, using high dose glutamate antagonist, and using less glutamate antagonist with some amounts of gabapentin.

© 2011 Published by Elsevier Ltd.

Introduction

Parkinson’s disease (PD) is a common progressive neurodegenerative disease that its main cause is the death of neurons in substantia nigra pars compacta (SNc) of basal ganglia (BG). The mechanisms of motor symptoms are not yet known in this disease and hence, there is no definite treatment for it. One of the most important symptoms of PD is gait disturbance which is especially present in severe states of the disease [1]. This is not an easy question to answer why PD gait disturbances are made up of several components such as slow gait, postural changes, festination and freezing of gait (FOG) [2].

One of the most unknown and unclear PD gait disturbances is FOG which is seen only in Parkinsonism. FOG is defined as an episodic inability to generate effective stepping in the absence of any known cause, other than Parkinsonism. This phenomenon refers to transient episodes lasting seconds (less than 1 min) in which walking is halted [3]. This symptom is a disabling condition which is annoying in elder subjects and can be a major mobility problem for the patients. This symptom is poorly treated by dopaminergic treatments [4], or very large doses of these drugs are needed to improve FOG [3]. FOG is not related to abnormal tone of muscles or its weakness, because after FOG episode, the subject is able to continue his normal gait. The severity of freezing is not correlated with any of the other cardinal features of Parkinsonism, supporting its unique and independent pathophysiology. PD patients with FOG have more stride to stride variability and show less symmetry between the left and the right sides of the body [1].

The pathophysiology of this phenomenon is more complex than that of the classic motor symptoms in PD. Freezing might be an independent cardinal sign of Parkinsonism. Even neuro-imaging methods are not able to distinguish the difference between FOG containing and FOG lacking patients. It seems that PD aggravation is the main cause of FOG. Barbaue realized that there is a significant increment in FOG beginning, nearly 1 year after using high dose Levodopa treatment [5], although it is not easy to diagnose if the cause of FOG is the aggravation of the disease or it is the side effect of the drug. A relation has been reported between FOG and dopamine antagonists in some studies [6]. It seems that using some tricks or sensory cues as rhythmic auditory stimulation may help the frozen patient to come out of FOG [7]. Some studies have showed the effectiveness of deep brain stimulation (DBS) on subthalamic nucleus and pedunculopontine nucleus [8].

Although different putative treatment strategies are proposed for FOG phenomenon, no absolute treatment is accepted. In this study, we will use mathematical models of PD gait to simulate FOG. With evaluating the changes in model parameters, we will try to propose some mechanisms for the pathophysiology of FOG. Finally some new treatment strategies will also be proposed for preventing this phenomenon.

Methods

We designed an artificial neural network (ANN) [9] model which simulates the behaviour of basal ganglia (BG) and produces stride time intervals. The structural parts of BG are shown in Fig. 1. The structure of ANN model is shown in Fig. 2. The feedback in layer one simulated the role of dopaminergic feedback of SNc. The direct and indirect pathways are modelled in the second layer. The output blocks of BG constitute the third layer of ANN. The last layer plays the
role of thalamus. The model is able to simulate the stride behaviour of normal and PD persons, based on changes in its weights. For training the network for normal and PD states, backpropagation training method was used. The model was trained and tested by real data of www.physionet.org and finally it was able to produce normal and PD states with mean square error less than 1%.

To simulate FOG, we completed the training phase to have a model which is able to produce an FOG episode in output signal. For this purpose, the weights of ANN were adapted to the new condition (presence of FOG). The weights which were changed markedly during the production of FOG were determined. These changes will be considered as the basis of FOG production in our hypothesis.

Finally, different therapeutic hypotheses were tested on the model to find the effective ones. This was done by changing the weights of the final trained model in order to find outputs which lack FOG.

Results

In Fig. 3 the response of the model for PD patient without FOG is presented. Considering an FOG in stride time interval signals, the response of the model for two states (FOG with 15 s duration) is depicted in Fig. 4. It seems that changes in dopaminergic weights (feedback weights in first layer) and biases resulted from dopaminergic neurons are significant. In these states, dopaminergic weights are decreased, but the biases are increased significantly.

In order to treat the produced FOGs, we decreased the input signal from the cortex and evaluated the response, which is presented in Fig. 5. It is clearly observable that FOG is deleted. In another test, we used glutamate antagonists in a high dose and showed that FOG is again deleted (Fig. 6). Since high dose of glutamate antagonist may have side effects, we reduced its amount and used low dose gabapentin simultaneously. The simulations showed that FOG is deleted again (Fig. 7).

Discussion

FOG is a disabling and troubling symptom of PD. Its pathophysiology is really unknown and complicated. In this study, we used the model of PD gait behavior for comparing normal and PD persons in order to simulate FOG and find its pathophysiology and probable treatments. For this purpose, two FOGs were simulated which had 10 and 15 s duration. The weights of the model were adapted to be able to simulate these FOGs. The amounts of weight changes in the adapted model were evaluated. We observed in the model that the dopaminergic weights were reduced in FOG producing state. This is physiologically plausible, as with progression of the disease, more number of SNc neurons are destroyed which leads to dopamine decrement. The increased severity of the disease is the result of reduced dopamine level.

Moreover, the amount of first layer biases which had dopaminergic feedback inputs, were increased in the model. In real PD patients, levodopa treatment causes resistance to this drug. The increased amount of bias in our simulation is similar to this increased resistance, because increased bias changes the neuron behavior from its linear region to the saturated one. This interprets why increasing the drug dose will not be effective in reducing the symptoms. Considering the results of the model, we can conclude that the main causes of FOG in higher stages of the disease are the severe reduction of dopamine in SNc and also the resistance of neurons to dopamine because of chronic high doses of the drug. This hypothesis is consistent with the beginning of FOG, nearly 1 year after high levodopa prescription [1].

FOG has no absolute treatment. Therefore, the model behavior was tested in order to find proper methods for suppressing the FOG. Based on our model three therapeutic strategies may be hypothesized:

1- Decreasing the cortex signal to BG will cause the deletion of FOG. It seems that during FOG, diverting the attention of the patients from walking has a proper role in eliminating the FOG episode. In clinical practice, some cueing methods had effective results on FOG, which is in accordance with this hypothesis [10].

2- Decreasing the glutamate effect by glutamate antagonist is another effective method. For this purpose, all the weights of the ANN which match with glutamate were decreased in our model. This led to elimination of FOG episodes in our output. This is seen in some clinical researches [11]. The
important point is that for effective decrement of glutamate on FOG, we need to use high doses of glutamate antagonists. This may have side effects on the patients.

3- With paying attention to the abovementioned strategy, we tried to diminish the dose. But for effective treatment of FOG, we needed some complementary drugs. In previous studies of the authors of this manuscript, the positive role of GABA on PD symptoms is presented [12]. Therefore, evaluation of its role on FOG treatment was considered. We suggest that less glutamate antagonist, with some amounts of gabapentin may be used concomitantly. Fig. 7 shows the effectiveness of this method. Using these two drugs with each other has not yet been reported in clinical practices.

In conclusion, we suggest that using physiologically plausible models in PD can be a proper preliminary method to evaluate the effect of different therapeutic routes on the symptoms of PD. We showed in this study that the main cause of FOG is probably severe decreased dopamine as well as increased resistance to dopaminergic drugs and using gabapentin with glutamate antagonist may be a relevant management for decreasing FOG episodes.

Sources

No source of support.

References


