Modelling of the Basal Ganglia Affected by Huntington's Disease

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Abstract

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder. The disease is due to a single gene which expresses huntingtin. Normal genes have less than 29 copies of the CAG trinucleotide repeat within each gene and mutant genes have an expanded number of CAG repeats. The disease affects initially the striatum and extends to other brain regions in later stages of the disease. A variety of the cellular processes are affected by the mutant gene and the cellular mechanism that links the mutation with the disease is to be found. This paper attempts to integrate hypothesis and experimental results into an integrated NEURON simulation framework, aiming to obtain a comprehensive understanding of the disease pathogenesis. The affected cellular processes that are considered include synaptic transmission, dendrite morphology change, transcription, and calcium signalling.

Key words: Huntington's disease, basal ganglia, striatum, GABA, glutamate, dopamine

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1 Summary

Huntington's Disease is an autosomal dominant neurodegenerative disorder characterized by uncontrollable involuntary movements, psychiatric abnormalities and dementia. The disease is due to a single gene which expresses Huntingtin and the disease mutation consists of an unstable expanded CAG trinucleotide repeat of the 5' coding region of the Huntington gene which encodes a stretch of polyglutamine. The cellular mechanism that links the mutation with the disease remains controversial.

Htt is expressed ubiquitously with highest levels in neurons of the central nervous system. The normal htt is present in nuclei, cell bodies, dendrites, and nerve terminals and htt is involved in clathrin-mediated endocytosis and functions in vesicle-transport processes in axons. Htt also organizes the post-synaptic density and modulates the morphology of dendrites and is involved in transcriptional regulation.

The disease affects initially the striatum and extends to other brain regions in later stages of the disease. Although this neurodegeneration constitutes the pathological basis of HD, considerable evidence has also shown that neuronal dysfunction occurs in the absence of neurodegeneration in the early stages of HD. Cognitive symptoms often appear before the onset of the other classical symptoms and postmortem studies show the absence of overt neuronal cell loss in early stage patients who had cognitive symptoms [1]. The molecular and cellular basis for selective vulnerability of the medium spiny neurons in the striatum in HD remains elusive.

One of the earliest neurochemical alterations observed is the loss of cannabi-

noid receptor binding from the basal ganglia nuclei. This loss appears to occur prior to the loss of co-localised receptors such as the dopamine D1 and D2 receptors [2]. Consistent with these findings, loss of CB1 receptor mRNA has been observed in the striatum of transgenic HD mice prior to the onset of motor related HD-like symptoms and preceding neural degeneration [3]. Disruption of axonal transport by pathogenis polyQ proteins could also contribute to early neuropathology in HD [4]

Studies of HD mouse models also provide compelling evidence that the N-terminal fragments of mutant huntingtin (htt) with an expanded glutamine repeat cause neurological symptoms resembling some clinical features of HD. Mutant htt inhibits the glutamate uptake in the HD mouse brain [5] and electrophysiological studies revealed a variety of abnormalities in neurotransmitter transmission in HD mice [6]. It is also found that mutant htt binds abnormally to synaptic vesicles and decreases the glutamate release in HD brain slices.

Early events in the disease cascade implicate enhanced NMDA receptor activation, with excitotoxity due to aberrant Ca^{2+} influx. It is demonstrated that these early phenotypes are associated with activation of the Akt pro-survival signaling pathway [7]. Ca^{2+} plays an important role in neuronal signaling and perturbed Ca^{2+} homeostasis is one of the key steps during initiation of the apoptotic program in affected neurons. [8] identified a novel molecular link between htt and InsP_3R1-mediated neuronal Ca^{2+} signaling and provide an explanation for the derangement of cytosolic Ca^{2+} signaling in HD patients and mouse models.

To integrate the different hypothesis and experimental results, we built up a model of the basal ganglia where the striatum is most affected by HD.

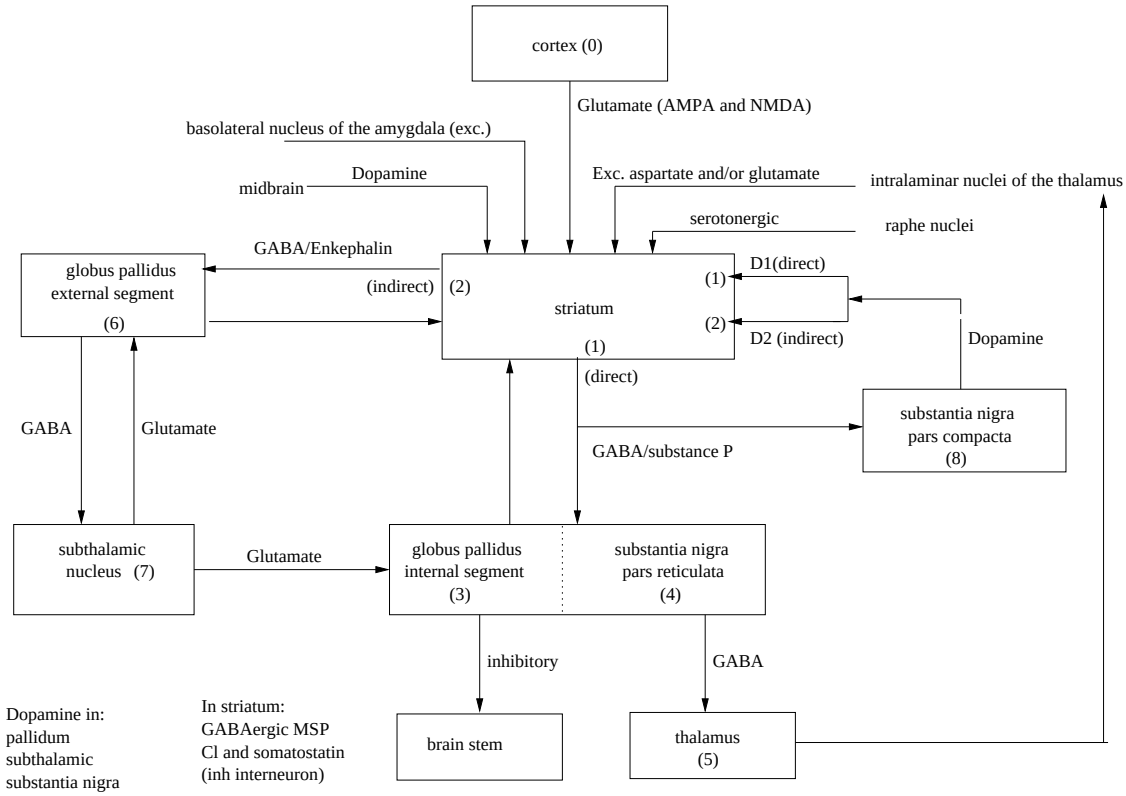

Fig. 1. Internal and external connections of the Basal Ganglia

The model was a large-scale biophysically-realistic model implemented in the software NEURON, a simulation environment for developing and exercising models of neurons and networks of neurons. Figure 1 shows the internal and the external connections of the basal ganglia and the neurotransmitters that are considered in the model. The striatum receives input from the cortex and thalamus etc and the output of the basal ganglia projects to thalamus and the brain stem. For the internal connections, we considered both the direct and indirect pathways. Most of the striatal neurons modelled are GABA-ergic medium spiny projection neurons and two types of striatal inhibitory interneurons are modelled: large cholinergic neurons and smaller cells that contain somatostatin.

Huntingtin's effect on the synaptic transmission is modelled by considering

the concentration and release of neurotransmitters glutamate (AMPA and NMDA), dopamine, and $GABA_A$ and $GABA_B$. The binding of dopamine receptors D1 and D2 are especially considered in terms of the experimental results mentioned above. Right now, we are adding to the model the cellular Ca^{2+} signalling pathway affected by mutant htt. Dendritic morphology change and the consequent change in neuronal information processing is being modelled too. We hope that, by putting these different pathological aspects of HD into an integrated framework, we will be able to better understand the pathogenesis of the disease, help with experimentalists to design new experiment paradigms and to develop therapeutic approaches to tackle the disease.

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Xiuxia Du received her bachelor and master degree on Electrical Engineering. She is now doing her Ph.D at Washington University in the area of computational neuroscience and systems biology, with a research focus on neuronal modelling and information encoding and decoding of turtle's visual cortex.

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