ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 2 Issue 4 April 2019

Review Article

Signaling Pathways Perspective of Neurodegenerative Diseases: Parkinson's, Alzheimer's, and Huntington's Diseases

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Received: February 8, 2019; **Published:** March 04, 2019

Abstract

In this paper it is given perspective in research of Parkinson's disease, Alzheimer's disease and Huntington's disease. These are slow progressive neurodegenerative disorders that have long lifespan, but with symptoms that can worsening over years and can appear in mid or late ages. Review of symptoms, hallmarks and causes are given for all three kinds of neurodegenerative diseases. Further, testing, drugs available, and 24 hours care are explored. These diseases are the result of brain impairments in certain regions of brain that are correlated to movement, speech, memory, learning, behavior, thinking and else. Nerve cells in these regions are damaged or dead which leads to difficulty in functioning. These diseases are followed with hallmarks. In case of Alzheimer disease these are amyloid plaques and neurofibrillary tangles. These hallmarks are further connected with cellular systems dysfunction and signaling pathways. It is interesting to set research framework to study signaling pathways and molecular mechanisms, and their crosstalk, in order to develop mathematical model and perform dynamical and bifurcation study of these pathways. The aim of research is to better understand the molecular mechanisms involved in Parkinson's, Alzheimer's and Huntington's disease, and to find the regulatory molecules and possible drug targets.

Keywords: Pathways; Neurodegenerative Diseases; Huntington's Diseases

Parkinson's disease

Parkinson disease a long-term neurodegenerative disease that affects part of brain called substantia nigra that controls movements of body [1]. Nervous cells in this area release dopamine, which is a neurotransmitter and controls the reflex actions. Disease attacks the nervous cells in this region, and they begin to die. Nervous cells cannot be replaced, and some percent of cell dies, symptoms like shakiness, tremors of hand etc. else starts appearing. It also has effects to normal behavioral activities like how you are walking, talking, sleeping or thinking. The symptoms become unnoticed in the beginning, but at certain point they are realized [2,3].

Parkinson's disease affected 6.2 million people in 2015 and resulted in about 117,400 deaths globally. Parkinson's disease typically occurs in people over the age of 60, of which about one percent are affected. Males are more often affected than females at a ratio of around 3:2.

The disease is named after the English doctor James Parkinson, who published the first detailed description of this disease in 1817. Worldwide day is also dedicated to Parkinson's disease.

Hallmarks of Parkinson's disease convert proteins into Lewy bodies in the neurons of midbrain part of substantia nigra.

Symptoms are related to movement: slow movements, tremors, walking and balance problems. Parkinson's can also cause a range of other issues, from depression to bladder problems. It affects the daily routine activities, but person can live near normal lifespan. It is important to know how to live whit with this disease. In later stages, it can cause dementia. Depression and anxiety are also common.

Even though Parkinson's can have a big impact on life, with the right treatment and help from health care team, patients can still enjoy the things they love. It's important to reach out to family and friends for support. It is important to learn to live with Parkinson's disease.

The causes of Parkinson's disease are genetical and environmental. Even if one has genetic predisposition, it does not mean that Parkinson's diseases appear. There is also risk for the people exposed to certain pesticides and among them with prior head injuries, while there is a reduced risk for tobacco smokers and those who drink coffee or tea.

There is no test for Parkinson's disease, therefore it is better if the symptoms are recognized early. There is no cure for the disease, but the symptoms are controllable by treatment. Hoehn and Yahr are used to tell what stage of the disease is have explained the ways to know stage of the disease. Drugs for Parkinson's can often help with tremors, stiff muscles, and slow movements. For treatment it these therapies may be used- physical therapy, occupational therapy, and speech therapy. In some cases, surgery is may also be performed.

Disease is slowly progressive, with up to 20 years needed to move from mild to more serious symptoms, but there are cases where change is faster.

Genes implicated in the development of PD include SNCA, LRRK2, GBA, PRKN, PINK1, PARK7, VPS35, EIF4G1, DNAJC13 and CHCHD2. SNCA gene mutations are important in Parkinson's disease because the protein which this gene encodes, alpha-synuclein, is the main component of the Lewy bodies that accumulate in the brains. Mutations in some genes, including SNCA, LRRK2 and GBA, have been found to be risk factors for "sporadic" (non-familial) PD. Mutations in the gene LRRK2 are the most commonly known cause of familial and sporadic PD, and are related to individuals with a family history of the disease and in sporadic cases. A mutation in GBA presents the greatest genetic risk of developing Parkinson's disease with risk increased 20-30-fold.

There is no perspective for significant new PD treatments soon. Currently active research directions include the search for new animal models of the disease and studies of the potential usefulness of gene therapy, stem cell transplants and neuroprotective agents. Here it is proposed research on signaling pathways study that influence accumulations of Lewy bodies as hallmarks of Parkinson's disease, or other abnormal proteins or gene mutations.

Defects in several cellular systems have been implicated as early triggers that start cells down the road towards neuronal death. These include abnormal protein accumulation, particularly of alpha-synuclein; altered protein degradation via multiple pathways; mitochondrial dysfunction; oxidative stress; neuroinflammation; and dysregulated kinase signaling. As dysfunction in these systems mounts, pathways that are more explicitly involved in cell death become recruited. These include JNK signaling, p53 activation, cell cycle re-activation, and signaling through bcl-2 family proteins. Pathways for Parkinson's disease are given in figure 1.

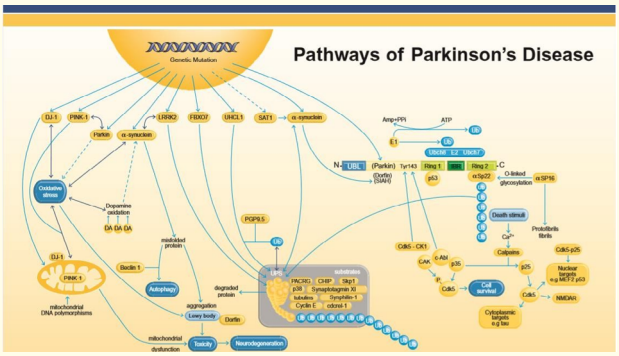

Figure 1: Pathways in Parkinson's Disease.

Further research will be focused on exploring these signaling pathways with mathematical modelling, and dynamical and bifurcation study [15,16], in order to investigate states, dynamics and possible drug targets for regulating abnormal proteins or gene mutations, and to revert normal functioning of cellular systems.

Alzheimer's disease

Alzheimer disease is slow progressive neurodegenerative disorder which appears people usually at the age of 65, but early onset can appear after 40 years of age. It prevents people from ordinary activity, social relationships, and it cause sharper intellectual fall. It is named after Alois Alzheimer who was the first person to study Alzheimer's disease. It is caused by the death of nervous cells in certain regions of brain. These physical brain impairments or damages are is followed by with intellectual and cognition fall, and loss of abilities. Alzheimer disease is followed by accumulation of amyloid plaques and neurofibrillary tangles in neural cells of brain, what leads to toxicity and cell dead. It is the most common type of dementia, accounting for 60 to 80 percent of cases of dementia in the United States. So far about 5 million people in the U.S. had been diagnosed with Alzheimer's disease. By 2050, the numbers are expected to double. Early-onset familial Alzheimer's disease can affect younger people with a family history of the disease, typically between the ages of 30 [5,6].

Hallmarks of Alzheimer's disease are extracellular amyloid deposits, intracellular neurofibrille tangles, cholinergic deficits,

synaptic loss, inflammation and extensive oxidative stress. The plaques are found between the dying brain cells, and they are made from a protein known as beta-amyloid. The tangles occur within the nerve cells, and they are made from another protein, called tau. These pathobiological changes are accompanied by significant behavioral, motor, and cognitive impairment leading to accelerated mortality.

There are several possible causes of Alzheimer's disease. It seems that Alzheimer's disease is caused by environmental, biological and genetic factors. If specific other diseases are present specifically, the risk is wider or higher. Scientists have discovered that many people with this form of the disease have a specific genes abnormality: mutation in genes located on chromosomes 1, 14, and 21. Furthermore, chromosome 19 contains a gene called apoE which helps in carrying cholesterol in the blood and in recovering nerves after injury. It is observed that people with apoE4 gene have increased risk of developing AD. In addition to genetic factors, many biological factors have been implicated in AD: for example, free radicals which are formed when the body metabolizes oxygen. Free radicals serve important functions - such as helping the immune system to fight disease. However, too many free radicals cause problems. It is observed that brain cells in AD produce the mutated form of amyloid protein and produce more free radicals. However, free radicals can also enforce beta amyloid protein production. Third, several environmental factors contribute to AD: aluminium as common contaminant in drinking water, since it is observed that both the plaques and tangles in AD contain aluminium. Important environmental factors are also zinc, smoking, high exposure to paint solvents, exposure to electromagnetic fields and power lines [7].

There is no single test for Alzheimer's disease. It can be detected by for signs and symptoms, medical history, and person's neurological function by testing their balance, senses, and reflexes. Other assessments may include a blood or urine test, a CT or MRI scan of the brain, and screening for depression.

There is no known cure for Alzheimer's. However, there are therapeutic treatment that can improve cognitive and behavioral symptoms. In order to treat AD drugs are developed and clinically tested. For developing a new drug, the research of 10-20 years is needed along with prior clinical tests and medical usage. The only allowable drugs today are so called cholinergic drugs as including tacrine, donepezil, rivastigmine, and galantamine. These drugs had limited success in treating AD. There is no definite way to prevent AD but maintaining a healthy lifestyle may reduce the = risk. This includes eating a healthy diet, losing excess weight, quitting smoking, getting regular physical activity (150 minutes per week), adding foods with omega-3 fats, such as salmon, to your diet or taking fish oil supplements, getting plenty of sleep, being socially active. Brain mental exercises can also improve cognitive function and lowers the risk.

In order to find relationship between of formation of amyloid plaques and neurofibrille tangles in Alzheimer's disease, molecular mechanisms or signaling pathways are studied. It is interesting to find what cause or influence normal or irregular functioning or signaling, and consequently formation of these neuronal physical abnormalities, alteration in function, or different cell function, what further leads to development of Alzheimer's disease. For that this reason, the research of signaling pathways that relate to Alzheimer's disease is being carried out by us. They cross talk with other molecular pathways or cause gene transcription that might lead to genetic mutation and alteration or change of cells functions or fate.

Signaling pathways are important in the regulation of the structure and function of the adult brain. It is found that activity of signaling pathways are present in the following areas of brain: frontal cortex, cerebellum, hippocampal formation, basal forebrain, and olfactory bulb. Damage or dysfunction of brain cells in these areas can cause many diseases. Alzheimer disease relates to impairment of learning and memory in basal forebrain, but this disease also attacks other areas of brain and consequently other functions. Research results with theoretical and experimental finding are reported in [12-14].

Several signaling pathways are connected to Alzheimer disease: AMPK pathway, mTOR pathway, Sirtuin1 pathway, PGC-1 pathway, and Wnt pathway. Short names are for biomolecules that play important role in cell. They are able to modulate several pathological events in AD. These include reduction of amyloid beta aggregation and inflammation, regulation of mitochondrial dynamics, and increased availability of neuronal energy. They can provide new therapeutics to slow down or prevent development of AD. These pathways normally increase transcription of genes that are important for normal functioning. For example, in case of dis-functioning caused by oxidative or inflammation insult, genes are transcripted in mitochondria to stabilize the functioning. It is important to reach greater understanding of the molecular basis of these pathways and ways how they interact within cell in order to slow down or attenuate metabolic deficits observed in AD. Examples of signaling pathways included in Alzheimer disease are shown in figure 2.

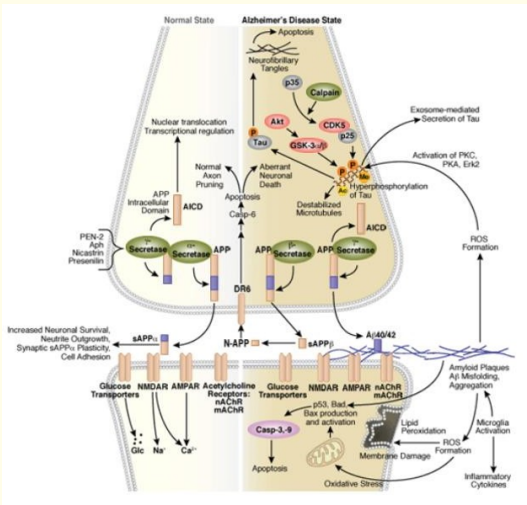

Figure 2: Signaling Pathways in Alzheimer's Disease.

It is important to consider the signaling pathways and to show which cellular processes are included. It is also of interests to show main components of the pathway. Further it is interesting to set up biochemical and dynamical model in order to obtain simulation results, perform dynamical and bifurcation analysis and to get insight into biological mechanism [15,16]. It is, question of further research to see what genes are transcribed and with what cell function, how it relates to proteins, genes, or other compounds in developing amyloid plaques and neurofibrillary tangles in Alzheimer's disease, and in order to find targets for potential drug development.

Signaling pathways found to effect Alzheimer's disease, are general pathways which are, found also to participate in biological processes that includes neurogenesis, axonal remodeling, formation and maintenance of pre and post synaptic terminals, and in excitatory synaptic transmission. It is also found in other human diseases such as cancer, metabolic diseases, coronary disease, diabetes and obesity, etc. From that reason, it is important to investigate signaling pathways and their coupling and crosstalk in order to better understand formation of toxic amyloid beta plaques and neurofibrillary tangles in Alzheimer disease.

It is interesting to examine connections between abnormalities, irregularities, and dysfunctions with physical causes of disease, in case of Alzheimer 's disease formation of amyloid plaques and neurofibrillary tangles. Further, it is important to discover what causes dysfunctions of signaling pathways, or how they fight against risks and factors that cause the disease. In further research it will be explored complexity and cross talk between the pathways and connection with diseases.

Huntington's disease

Huntington's disease (HD) or chorea is inherited neural disorder that typically appear in 30- 50 years of age and results in neuronal damage and death of brain cells. Main symptoms are subtle changes in personality, mood or mental problems, cognition, lack of coordination, unsteady gait, uncoordinated jerky body movement, physical skills, difficulties to talk, and dementia. The most characteristic physical symptoms are jerky, random, and uncontrollable movements called chorea. Specific symptoms and difficulty levels vary with people [8].

Huntington's disease is first described in 1841 by Charles Oscar Waters, but in further detail in 1872 by George Huntington, after whom it is named. Genetic bases were discovered in 1993 by collaborative research led by Hereditary Disease Foundation.

Huntington's disease is in most cases inherited from parents, but in certain percent can also be caused by new mutations. The cause of disease is gene mutation called huntingtin. Mutation causes abnormal protein formation, which further damages cells in brain through mechanisms that are still unknown.

Diagnosis of Huntington's disease is made through genetic testing. There is no cure for Huntington's disease. In later stages of disease full time care is needed. Some treatments, like tetrabenazine can relieve symptoms and improve quality of life. Disease affects men and woman equally. Complications can be caused with pneumonia, heart disease, suicide or physical injury.

Current research includes determining the exact mechanism of disease.

Physical symptoms are chorea which may be initially exhibited as general restlessness, small unintendedly initiated or incomplete motions, lack of coordination, or slowed saccadic eye movements. These minor motor abnormalities usually precede more obvious signs of motor dysfunction after three or more years. As disorder progresses, it there appears rigidity, writhing motions, or abnormal posturing, physical instability, abnormal facial expression, and difficulties in chewing, swallowing, and speaking, eating difficulties, sleep disturbances, seizures and other [9,10].

Cognitive abilities are progressively impaired. Especially affected are executive functions, which include planning, cognitive flexibility, abstract thinking, rule acquisition, initiation of appropriate actions, and inhibition of inappropriate actions. Further, memory

deficits appear, short-term and long-term memory deficits, episodic, procedural and working memory deficits. Cognitive problems lead to dementia.

Neuropsychiatric manifestations are anxiety, depression, a reduced display of emotions, egocentrism, aggression, and compulsive behavior, the latter of which can cause or worsen addictions, including alcoholism, gambling, and hypersexuality. They also have suicidal thoughts and suicide attempts. Individuals have reduced awareness of chorea, cognitive and emotional impairments.

Mutant gene Huntingtin is expressed throughout the body and associated with abnormalities in peripheral tissues that are directly caused by such expression outside the brain. These abnormalities include muscle atrophy, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, and testicular atrophy.

In study of signaling pathways and their crosstalk involved in Huntington's disease it is interesting to set mathematical model and perform dynamical and bifurcation study [15,16]. It is also interested to find regulating molecules and possible drug targets. Signaling pathways found in Huntington disease are Golgi stress signaling pathway, ERK pathway, Ca2+ and CAMP signaling pathway, JAK/STAT signaling, insulin signaling pathways and others. Examples of signaling pathways included in Huntington disease are given in figure 3.

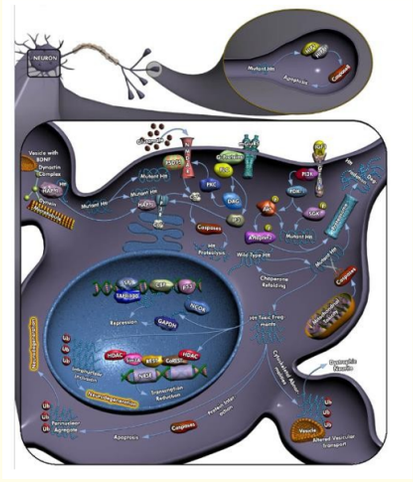

Figure 3: Signaling Pathways in Huntington's Disease.

This research will lead to better understanding of molecular mechanisms and signaling pathways and might relieve regulating molecules and help in finding possible drug targets.

Conclusion

In this paper there are reviewed three main neurodegenerative diseases – Parkinson's, Alzheimer's, and Huntington's disease. These diseases influence impairments in movements, learning, memory, behavior, thinking and else. Here are reviewed symptoms and causes of diseases, and hallmarks that physically effects nervous cells or brain are stressed. Environmental and genetic causes of diseases are reviewed. It is of interest to explore biological mechanisms and signaling pathways involved in these diseases and their crosstalk. It is further of interest to find regulating molecules and possible drug targets in order to develop drugs and help in curing disease. For that reason, it is firstly needed to set mathematical models and perform dynamical and bifurcation study of biological mechanisms or signaling pathways in order to understand main molecules involved in, triggers, and outcomes. Changes in bifurcation parameters can help to understand and show change of cells dynamics and corresponding cell states functions and outcomes. This research is expected to help in understanding the diseases and signaling pathways involved, and to help in finding drug targets.

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Volume 2 Issue 4 April 2019