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Research Article

Signalling Pathways Coupling in Alzheimer Disease

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Abstract

Signalling pathways are important in the regulation of the structure and function of the adult brain. It is found that activity of signaling pathways (ex., Wnt) 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. Here we are concerned with Alzheimer disease, which is connected with impairment of learning and memory in basal forebrain, but this disease also attacks other areas of brain and consequently other functions. Hallmarks of Alzheimer disease are formation of toxic amyloid beta plaques and neurofibrillary tangles that leads to neural cell death or prevent normal function of cell. In this paper we are concerned with different signaling pathways and their coupling which is found to be connected with Alzheimer disease. It is indirectly or directly connected with formation of plaques or tangles. One approach of Alzheimer Disease study is through computational modeling and dynamical study of bifurcation, stability and other dynamical properties of system. In order to accomplish this set of biochemical reactions of signaling (with coupling or not) that underly this signaling is set, for which we derive consequent dynamical model. Based on the experimental data from the literature simulations, computational investigation, and dynamical analyze can be done. Through this approach key acters and molecules included in the pathways (with coupling or not) can be found, where we look for the regulating molecules as possible targets for drug development. Signaling pathways found to effect Alzheimer disease, are as signaling pathways in general, found also to participate in diverse 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.

Keywords: *Alzheimer Disease; Crosstalk of Signaling Pathways; Dynamical Analyze and Bifurcation; Computational Model*

Introduction

Alzheimer disease is followed by accumulation of amyloid plaques and neurofibrillary tangles in neural cells of brain, what leads to toxicity and cell dead. These physical brain impairment or damage is followed with intellectual and cognition fall, and loss of capabilities. Beneath these impairments is production of amyloid beta protein and tau protein, that is interfered with signalling pathways that provide important functioning to organism, cells, or central nervous system, like cell proliferation, differentiation, adhesion, survival, and apoptosis, as an examples of functions that are provided with Wnt signaling pathway. Other pathways found to be included in pathology of Alzheimer's disease are AMPK, mTOR, Sirtuin1, and PCB-1. They crosstalk with other molecular mechanisms, biological functions, and cell signaling in normal cell functioning and in disease. However, disease appears in case of abnormalities, irregularities or dysfunctions. Causes of Alzheimer disease are environmental, biological, or genetics factors. It can be also triggered earlier if other diseases are pres-

ent like pneumonia, diabetes, injuries and strokes, HIV, or other specific diseases. It is interesting to examine connections between these abnormalities, irregularities, and dysfunctions with physical causes of disease, in case of Alzheimer 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 we will explore complexity and cross talk between the pathways and connection with diseases. As example of signalling pathway that is included in Alzheimer disease we take Wnt signaling *pathway* since it has important cell functions, and cause transcription of genes that provide normal functioning and also have protective and neuroprotective effect in preventing and fighting off risk factors of disease. Wnt signalling is also found in other human diseases such as cancer, metabolic diseases, coronary disease, diabetes and obesity, etc. Our aim is to set framework for research examination of Alzheimer disease via understanding molecular mechanisms, biochemical reactions and mathematical modeling, and in future to perform dynamical analyze with simulation results, stability and bifurcation tests, in order to get better understanding of signaling pathways and connection with diseases.

Materials and Methods

Alzheimer disease is neurodegenerative disorder which appears in people 65 years old or older, but early onset can appear after 40-ies. It prevents people from ordinary activities, social relationships, and it cause sharper intellectual fall. It is named after Alois Alzheimer who was the first to study Alzheimer desease. Disease can be confirmed only after autopsy, and in living person it is only diagnosed as "probable Alzheimer desease". It is similar with dementia or senile dementia, but pathological and functional signs and brain damage in Alzheimer desease is much harder [1].

Alzheimer desease is followed with neuropathology which signs are accumulated amyloid plaques on extra cellular surface of brain cell and neurofibrille tangles inside brain cell, that prevents brain and neuronal cells form normal functioning. Amyloid plaques and neurofibrille tangles presents specific physical abnormalities in brain.

Alzheimer desease is progressive, what means that simptoms are worsen when desease advance. The earlies simptoms of Alzheimer desease are mild memory loss, forgotten last conversation data, or what year is. It can be present some form of desorientation, problems with routine tasks, changes in personality, or in judgment. As desease progresses, simptoms get worse in everyday life, so 24 hour help is needed. It can be present anxiety, suspiciousness and agitation, wondering, difficulties in recognizing members from close family or friends, and dream disturbances. In more advanced form, patinent loss ability to talk, have weight and appetite loss. It is not directly fatal, but it can leave patients with desease over deacades. It can also cause infections and other deseases like pneumonia which can be ultimate cause of death. Often, people are exausted and die earlier, but patients which are normally healty can survive over decades.

Alzheimer desease is characterised with anatomical changes that forms amyloid plaques and neurofibrille tangles that can be perplexed. Tangles and plaques prevents normal functioning and different functions of neurons and neuronal cells in brain, what causes general slowlyness and loss of capabilities. Amyloid plaques are formed, sticked, and accumulated on extracellular side of neuronal cell in brain. Amyloid is protein that is normally present in whole body. In AD it is inequaly divided creating the substance called beta amyloid that is toxic for nerve cell. As amyloid plaques are accumulated brain cells starts to die. Neurofibrille tangles which can be perplexed are second anatomical sign of Alzheimer disease. Normally, each cell in brain contain long fibers made from proteins which serves as scaffold and supports brain cell in right form. It also helps in transport of food materials and nutritients in cell. In AD these fibers starts curling and clewing. Brain cell lose its form and becomes uncapable to transfer food and nutritients in right way, what cause cell to eventually die. As plaques and tangles are accumulated in brain, wide cells dying in brain is present.

There are reported several possible causes in development of AD. It seems that Alzheimer disease is caused environmentally and that biological and genetic factors are included. If specific other diseases are present 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: aluminum as common contaminant in drinking water, since it is observed that both the plaques and tangles in AD contain aluminum. Important environmental factors are also zinc, smoking, high exposure to paint solvents, exposure to electromagnetic fields and power lines.

Alzheimer disease can also be developed in patients who already have some disease, like injuries, pneumonia, diabetes, strokes, viral infections, HIV, or other. It is important to conduct research to find relationships with these and other diseases. Environmental factors can trigger Alzheimer disease or cause symptoms to appear earlier. Currently, much more research is needed to identify other triggering factors, and to learn what can be done to prevent it.

In order to treat AD drugs are developed and clinically tested. It is needed 10 - 20 years of research of new drug, prior clinical tests and medical use. The only allowable drugs today are so called cholinergic drugs as tacrine, donepezil, rivastigmine, and galantimine. So far, these drugs had limited success in treating AD. Tacrine causes side effects and is rarely prescribed. Aside of cholinergic drugs, researchers looks for other kinds of drugs that can influence other chemicals in brain, or which interfere with forming plaques or tangles in AD, or enforce brain activity for producing new neurons in order to substitute dead neuronal cells. Also, dietal supplements can help, prevent or slow AD. Damage in brain caused by free radicals can be treated with antioxidants that can be found in Vitamin C, E, beta carotene which is associated to Vitamin A. Other antioxidants found are ginko biloba and phosphatidylserinme. However, supplements with high dosage of antioxidants can cause specific side effects. Safer way in consuming antioxidants is by diet, taking fruits and vegetables, brown rise, integral grain, meat, eggs, and milky food. It can be also used anti flammation drugs like aspirin or pain releif drugs.

It is unclear so far why plaques and tangles starts to form in AD brain. Many researchers try to answer these questions and try to develop ways of preventing or healing this neurodegenerative desease. Last researches discovered vacine that promise preveting and treating of AD since it has possibility of solubility of plaques. However, it is still not found vacine which will dissolution or solve problems with tangles which is considered to have complicated role in AD [1].

Research of AD is actual today, but it is considered that will be needed years or decades to solve this problem and to find drug for people altered or ill from AD. In order to find relationship of formation of amyloid plaques and neurofibrille tangles in Alzheimer disease research is conducted to find molecular mechanisms or signalling pathways that cause or influence unnormal or irregular functioning or signalling, what consequently cause formation of these neuronal physical abnormalities, alteration in function, or different cell function, and what lead to development of Alzheimer disease. For that reason we present findings of signalling pathways that are connected with Alzheimer disease. They cross talk with other molecular mechanisms, signalling pathways, or cause gene transcription that might lead to genetic mutation and alter or change cells functions or fate. Irregularity or dysfunction of signalling pathways can cause AD related problems. Signalling pathways can also act neuroprotectively to neural cells in brain, or heal them after injury or take off the risks if they are attacked.

Alzheimer disease is characterized with progressive loss of cholinergic neurons that lead to severe behavioral, motor and cognitive impairments. Extracellular amyloid beta plaques and neurofibrillary tangles containing hyper phosphorylated tau are frequently present in brain of patients with AD. Energy failure in neurons and brain in AD is also hallmark of this disease. Energy demands are prerequisite for neuronal communication. It is a question what causes these impairments, energy failure and accumulation of amyloid plaques and neurofibrillary tangles?

In order to answer this question there are attempts to discover metabolic pathways that might lead to pathogenesis of AD. So far, several signaling pathways are discovered, with attempts to discover mechanism behind these pathways: AMPK pathway, mTOR pathway, Sirtuin1 pathway, PGC-1 pathway, and Wnt pathway (name derived after *wingless* gene in *Drosophila*). Short names are for biomolecules

that play important role in cell [2,3]. 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 [1]. They can provide new therapeutic 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.

In considering crosstalk of signaling pathways we are interested to show which cellular processes are included and to show main components of the pathway. Further we are interested to set up biochemical and dynamical model in order to obtain simulation results, perform dynamical and bifurcation analyze and to get better insight into biological mechanism. 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 developing Alzheimer disease, and in order to find targets for potential drug development.

Molecular mechanisms are still unclear with several genes or proteins associated that leads to Alzheimer disease. In research we are interested to present clues on how to determine and investigate pathways included in Alzheimer disease. For modeling we use computational approach that is presented with biochemical and mathematical framework for dynamical analyzing of signaling pathways. More complex problems will be focus of further research, since thorough investigation of the results from literature is needed.

Signaling pathway (ex. Wnt) are involved in several key cellular processes associated with cell proliferation, differentiation, adhesion, survival, and apoptosis in several catabolic and anabolic cells, including neuronal and glial cells which are key residents of Central Nervous System.

Results and Discussion

Our aim is to thoroughly understand Alzheimer disease and to connect formation of amyloid plaques and neurofibril tangles as hallmarks of Alzheimer disease with signaling pathways and their possible crosstalk. Biochemical and dynamical modeling of these signaling pathways and their coupling with bifurcation and dynamical analyse can help in determining key molecules/factors that are connected with this disease and to provide clues for possible drug targeting [4-8].

Conclusion

Alzheimer disease is followed by accumulation of amyloid plaques and neurofibrillary tangles in neural cells of brain, what leads to toxicity and cell dead. Beneath these impairments is production of amyloid beta protein and tau protein, that is interfered with signalling pathways that provide important functioning to organism, cells, or central nervous system, like cell proliferation, differentiation, adhesion, survival, and apoptosis. Alzheimer disease can be caused with environmental, biological, and genetic factors. It can be also triggered earlier if other diseases are present like pneumonia, diabetes, injuries and strokes, HIV, or other specific diseases. Formation of amyloid beta protein and tau protein is found to be connected with dysfunction of signaling pathways. Signaling pathways found to be included in pathology of Alzheimer's disease are Wnt, AMPK, mTOR, Sirtuin1, and PCB-1 signaling. They crosstalk with other molecular mechanisms, biological functions, and cell signaling in normal cell functioning and in disease. Disease appears in case of abnormalities, irregularities or dysfunctions signaling pathways or biological mechanisms, or accumulation of irregular proteins.

We are interested in setting research framework to determine what signalling pathways are included with Alzheimer disease and how they are connected with formation of amyloid plaques and neurofibrille tangles. To determine key actors and regulating molecules through which functioning of signaling pathways can be improved or to find possible drug targets if biochemical treatment is needed. Our approach is through computational study (biochemical and dynamical modeling) and bifurcation and dynamical analyze of dynamical model of signaling pathways and their crosstalk.

In future research we expect more results and key conclusions of causes and treatment of Alzheimer disease.

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Conflict of Interest

No conflict of interest.

Bibliography

1. Alzheimer disease.

2. Godoy JA., *et al*. "Signalling pathways crosstalk in Alzheimer's disease". *Cell Communication and Signalling* 12 (2014): 23.

3. Vallee A and Lecarpentier Y. "Alzheimer disease: Crosstalk between canonical Wnt/beta catenin Pathway and PPAR Alpha and Gamma". *Frontiers in Neuroscience* 10 (2016): 459.

4. Mitrasinovic O and Kablar NA. "Computational approaches in preclinical diagnostics and prognosis for Alzheimer disease". *Alzheimer and Dementia* 13.7 (2017): 1005-1006.

5. Mitrasinovic O and Kablar NA. "Emerging computational strategies identify MyD88 as downstream target in interleukin-1α induced signal transduction in alzheimer's disease". *Alzheimer and Dementia* 5.4 (2009): e21-e22.

6. Mitrasinovic O and Kablar NA. "P3-366: Indirect neuroprotective effects of interleukin-1α in the hippocampal ex vivo organotypic co-culture model". *Alzheimer and Dementia* 4.4 (2008): T628-T629.

7. Kablar NA. "Mathematical Model of IL-1-NFkB Biological Module". *Global Journal of Mathematical Sciences* 1.1 (2012).

8. Kablar NA. "MAPK Module: Biological Basis, Structure, Mathematical Model and Dynamical Analyse". Proceedings of the 19th International Symposium on Mathematical Theory of Networks and Systems - MTNS 2010, Budapest, Hungary (2010).

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