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Review Article

Experimental Models for Elucidating the Pathogenesis of Alzheimer's Disease: A Brief Review.

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ABSTRACT

Alzheimer's disease (AD) is one of the leading factors of dementia and other cognitive problems despite that there is no curative treatment for the cure of that disease currently. This is mainly due to the pathological features of disease accompanied by the extracellular senile plaques and also the intracellular neurofibrillary tangles which leads to synaptic as well as neuronal loss. This feature occurs prior to memory loss which is irreversible and becomes severe at the stage of clinical diagnosis. At this stage experimental models of AD proved to be better tool in achieving some of the novel therapeutic approaches and also in the development of pathogenic knowledge about the disease. The most commonly used animal model is APP transgenic mice. This model directly corelates the accumulation of senile plaques leading to the disease by expressing the genes associated with the familiar AD. This experimental model proved to be a useful tool for therapeutic screening. Although these models are not highly efficient in revealing the disease but they gave us an insight idea about the pathological changes which occur in AD. In this report we will discuss about the different models used and how they are helpful in revealing the pathogenesis of AD.

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INTRODUCTION

It is the brain neurodegenerative disorder associated with dementia (Adav SS and Sze SK, 2016). It has so much influenced the society that it has become the fourth leading cause of death in just a short era. Clinical symptoms associated with AD are impaired movement, mood disability and change in personality. This disease was first time discovered by Alois Alzheimer in 1906 in the

patient Augustine deter. In him he found some kind of mental illness accompanied with hallucinations, delusions and cognitive impairment. Pathophysiological cause of this illness came into light by doing histopathology of that patient brain which confirms the presence of senile plaques and the neurofibrillary tangles in the cerebral cortex responsible for the neuronal cell death and causing mental illness (Selkoe DJ, 2004; Blessed G et al, 1968). Basically, in Alzheimer neurodegeneration is attributed to extracellular formation of amyloid beta which further causes the formation of senile plaques and intracellularly the phosphorylation of tau protein leads to fibrillation of tangles forming neurofibrillary tangles (NFT). These all-pathological changes cause the synaptic to dysfunction and cortical atrophy thus, leading to neuronal cell death. It is not always necessary that these pathological changes take place before the appearance of symptoms. They can also take place earlier providing us the implementation time for the strategies to target the target for the treatment of AD. Age is the main factor affecting the occurrence of the disease. With increase in age, the progression of Alzheimer also takes place. It becomes double at the age of 65 and 50 percent chances are there at the age of 85 (Alzheimer's A, 2015).The probability of AD does not depend upon the gender. It has equal probability of occurrence whether it's a men or women. Genetic factors also play a major role in the pathogenesis of AD. They are down syndrome, mutation in the presenilin gene and expression of the apolipoprotein (APOEe4) allele. Some of the AD forms were the result of gene mutation. This led the researchers to develop genetically modified animals that could be helpful in depicting the features as well as the pathogenesis of AD. They are also useful for testing new therapeutics in preclinical trials. Various models were developed with the help of genetic technology to depict the pathogenesis of Alzheimer. the models developed were transgenic, non-transgenic and in-vitro models. Transgenic models consist of APP transgenic mice in which the mutated amyloid precursor protein(APP) gene is inserted which clearly depicts the correlation of senile plaques with Alzheimer's. another model named tau transgenic mice also shows the formation of NFTdue to the mutation in the tau protein related gene expression (Lewis J et al, 2001). Non transgenic model consists of high fat diet(HFD) induced model in which high fatty diet induced hypercholesteremia responsible for the inflammation accompanying the AD. The in-vitro models are followed by cell model and tissue model which proved to be of greater advantage and efficient method in studying the pathogenesis of AD (Gong CX et al, 2001).

PATHOGENESIS

The age of onset as well as the rate of occurrence varies from person to person owing to its complex and multifactorial nature. In this basically degeneration of neurons takes place accompanies with many histological changes in brain. Neuron's degeneration takes place mainly due formation of extracellular senile plaques and intracellular neurofibrillary tangles formation. amyloid precursor protein responsible for neuron growth and repair undergo breakdown by amyloidogenic pathway. In the presence of beta and gamma secretase amyloid gets break down into amyloid monomers and then aggregate to form oligomers. This oligomers accumulation leads to dysfunction of neurons and ultimately leading to their degeneration (Park SA et al, 2009). Normally, this amyloid beta breakdown takes place by phagocytosis by microglia or with the help of protein nephrilysin, so any change in these activities leads to formation of amyloid oligomers and later on their accumulation leads to AD. Second main pathological reason for the AD is formation of NFT. Basically, micro-tubules are responsible to from cell highway to transport cellular production from soma to axon terminal followed by retrograde and anterograde pathway. Tau protein is responsible for the stabilization of these micro-tubules during, AD amyloid beta activates protein kinase which phosphorylates the tau protein leading to its detachment from the microtubule and causing them to dissemble and itself form NFT (Blasko

I et al, 2004). These tangles disrupt the transport mechanism and neurons begin to die. Many genetic factors are also responsible for the aggravation of the above pathological causes like

- Down syndrome
- Mutation in the pre senillin 1 2 genes (Obulesu M et al 2011)
- Inheritance of the APOE e4 allele (Sing CF and Davignon J, 1985)

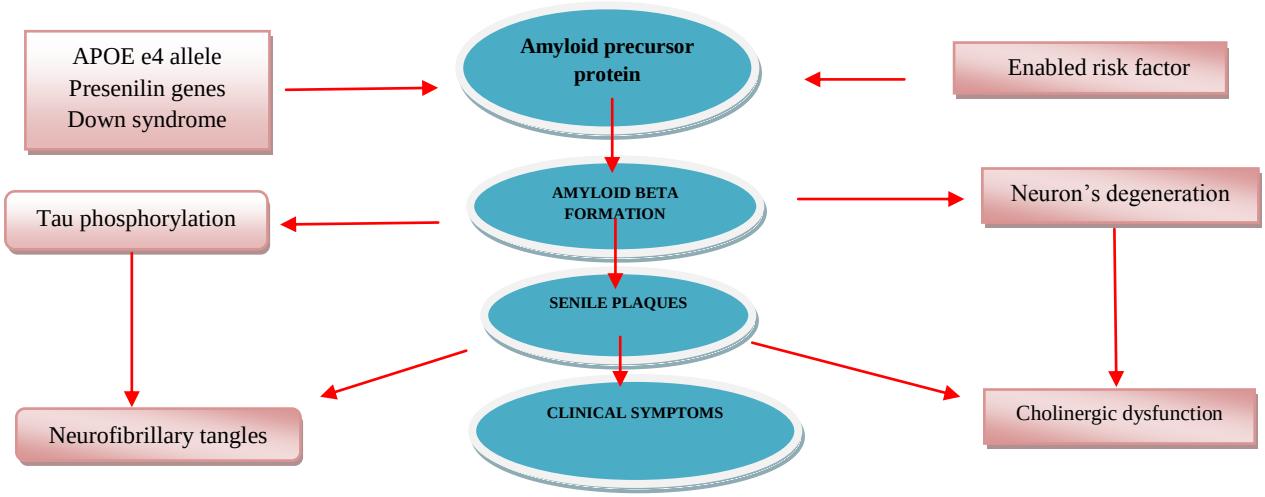

Fig.1: **Schematic design of pathophysiological cascade of Alzheimer 's disease**

In this pathophysiological cascade flow chart, it is clearly depicted the main cause of AD and the various other factors contributing to aggravate these pathophysiological causes. Also, it clearly represents the various genetic factors contributing as one of the major causes in developing AD. The genetic factors like down syndrome in which trisomy of 21st chromosome takes place which is responsible for the expression of genes responsible for the AD.

ETIOLOGY

AD destroys the neurons of the brain that control the memory, including the hippocampus which controls the short-term memory leading to short term memory failure. Later it affects the cerebral cortex responsible for language and reasoning with the loss in ability to make judgments (De Souza LC et al, 2014). Personality changes also occur which basically include emotional out bursts, wandering and agitation (Bateman RJ et al, 2012). Slowly many other areas of the brain get involved, the brain shrinks and losses functions thus making the person bedridden with major health issues.

EXPERIMENTALMODELS

Experimental models play a major role in understanding the pathogenesis and also for the preclinical testing of therapeutics. Between a vast majority of animal models, transgenic mouse is mainly used in depicting the pathogenesis of disease by expressing the human genes responsible for the amyloid beta plaques formation. The gene responsible for plaque formation is human APP and for the tangles it is human microtubule associated protein tau (MAPT) (Boutajangout A and Wisniewski T, 2014). Animal models basically explicit the changes occurring in the AD proving as an advantage over the in vivo models that limits the accessibility to the tissue and prevent real time measurement of biological changes associated with the disease. Consequently many in vitro models have been developed so that the in vivo models can also be a useful tool for us. All these models are helpful in depicting the underlying cause of AD and also used in testing the differenttargets against the disease (Shibata T and Wada K, 2011). Side by side a researcher should also have the good knowledge of the neuropathy so that he can accurately corelate the pathological

changes observed to human AD.Therefore, in this report we will basically discuss different types of models used and also their features and the limitations of using these experimental models in studying the pathological changes of AD. There are three types of experimental models.

- Transgenic model
- Non-transgenic model
- In-vitro model

Transgenic Models

The knowledge of genes related to AD led to the formation of many transgenic models either by transferring a gene into the existing the genetic makeup or by modifying genes using genetic technology. Mice are the most commonly used transgenic animal due to their easy manipulation and accessibility (Unger Lithner C. et al, 2011). Sometimes rats are also used although they are not widely available. The different types of models are described below

APP Transgenic Model

The first transgenic models used were APP to explain the function of senile plaques by expressing a transgene of human APP. Initially when the experiments were performed only the formation of amyloid beta was seen but no senile plaques were depicted. This led to a suggestion that there is not anycorrelation between cognitive disorder and senile plaques (Quon D et al, 1991). It was mainly due to low expression of the APP gene. More effort wasmade to proof the above correlation to a positive view. In recent studies a different type of APP taken, this time it was associated with a platelet growth factor and the result was as expected. The formation of senile plaques was observed along with the synaptic loss (Games D et al, 1995). This led the scientist to make more effort in this field. They develop other transgenic models by taking the alternate gene of interest. Mainly, Tg2576 and APP 73were used showing the loss in cerebral region along with learning deficitTg2576 was observed with a 5-fold increase in senile plaques in just around 8 months and APP23 with 14-foldincrease in just around 6 months (Hsiao K et al, 1996). Another model TgAPP also depicts the plaques in the olfactory bulb, thalamus and hypothalamus at an early stage. These all findings correlate the senile plaques and Alzheimer but not the involvement of NFT which act as a limitation on these models but beside that they provide valuable tools foramyloid beta modifying drugs (Richards JG et al, 2003).

TAU Transgenic Mice

These models were used to find the role of tau protein in the pathogenesis of AD. Based on the 6 isoforms of tau protein in our body different tau protein models were formed (Lewis J et al, 2001). A model named P301L with 4 times tau protein repeat along with a promotor was studied. It was found that tau protein level increases in the motor cortex of spinal cord but no NFT formation was observed. Another models Thy tau 22 with 2 mutations at G272v and P301S along with a promotor thymine 1.2 was used (Schindowski K et al, 2006). This time synaptic dysfunction along with its loss was observed. Also, the new observation came into light which was the appearance of NFT in hippocampus. The role of glial protein was also observed in the occurrence of fad AD. This directly link the formation of NFT as one of the pathogenesis cause AD (Forman MS et al, 2005).

APP/ TAUDouble Transgenic Mice

Till now, we depict the corelation of APP and tau protein as the cause of AD but the relationship between APP and TAU was not established, so. To directly relate the APP and tau, these models were used (Braidy N et al 2012). To study these models a transgenicmice carrying both the APP and tau protein genes is to be needed. This is done by crossing the APPTg2576 and VLWharton hall lines expressing human mutant was done resulting in the formation of transgenic mice. When this model was under observation study it was found that it contains 7-fold increase in tau protein and accumulation of A beta in olfactory and amygdale (Janelsins MC et al, 2005). This was great discovery as it directly corelates the different factors playing a key role in the pathogenesis of AD. This modelstudy led to the further detailed study of the models for the potential target for AD treatment.

Triple Transgenic Mice

In this model we took a transgene mice carrying variant gene like APP, pre senillin(PS1) and tau which develop extracellular amyloid beta deposits in an early span of 6 months observed in the main regions like hippocampus and neocortex. Approach of this model was done due to same output of the simple APP mouse model and double transgenic mice reflecting the insufficiency of the model for the disease (Ruiz-Opazo N et al, 2004). So, a need arises to develop a model in which the output in comparison to the simple APP model.

Transgenic Rat

Rats were chosen over the mouse due to many reasons. They were highly rich in genes and well characterized behaviour. They are also very close to humans with respect to genetically and physiologically. Transgenic rat model containing wide type APP gene was used as the first model which depict only the formation of amyloid beta deposits lacking the senile plaques (Do Carmo S and Cuello AC, 2013). But again, with the help of the PSI gene the expected outcome comes with the occurrence of senile plaques along with amyloid deposits. Many efforts were done to study the models in rat but due to some limitation it was not fruitful. The embryonic cells are difficult to acquire and a lot of cautions are to be taken while performing the experiment (Sodhi RKet al, 2014).

TABLE 1: Transgenic Models used for Pathogenesis of AD.

Transgenic models	APP	APP23 TG2576 PGF – APP TgAPP	Amyloid beta was seen. Also, the cognitive and behavioural impairment is observed	No tau protein and NFT were seen.	(Quon D et al, 1991) (Hsiao K et al, 1996) (Games D et al, 1995) (Richards JG et al, 2003).
	TAU	P301L Thy tau	Tau tangles can be seen with the motor impairment	No effect of APP is seen	(Schindowski K et al, 2006)
	APP\TAU double transgenic mice	APP\TAU	Both the beta plaques as well as tau tangles are visible	Same amount of Aβ is seen as in case of single APP	(Braidy N et al 2012) (Janelsins MC et al, 2005)
	APP triple transgenic mice	3×TgAPP	More severe pathology linking with human AD	Plaques are developed slowly	(Ruiz-Opazo N et al, 2004
	Transgenic rat	PSIAPP	Well characterized as compared to mice	Can't depict all the pathological characteristics of AD.	(Do Carmo S and Cuello AC)

Non-transgenic Models

Natural Models

Various animals are used as natural model ranging from rodents to non-human primates which spontaneously show the AD related

neuropathology as well as the cognitive impairment. As the first criteria for AD wad the memory loss (Solà C et al, 1993). Basically, the aged animals were used as the natural models which after studying have proved to be a valuable tool in depicting the natural pathology of AD. Rodent owing to its simplicity and ease to obtain made their use in large number. As we have already studied the use of nephrilysin and the protease enzyme in the amyloid beta degradation (Gonzalo-Ruiz A et al, 2003). Rats have also been used to depict the effect of AD on the neurons which may be cholinergic or glutamic (Beck M et al, 2003). along with effect of other environmental factors.Other animals such as gerbil and guinea pigs also follow the same pathway for the degradation of amyloid precursor protein but no occurrence of the pathological changes such as amyloid beta deposits and NFT (Chen Y et al, 2014). were seen which act as a limitation on the use of these model. Other model frequently used as natural one was senescence accelerated model (SAM) clearly showing the pathology features of AD. These were selected on the phenotypic variation from the nine accelerated mice prone to variation.

High Fat Diet

This model was made in use based on the role of cholesterol in the development of AD. The role of cholesterol in the removal of amyloid beta is known. HFD is highly related to AD as it raises the level of cholesterol in the body as it is directly corelated to serum and cerebral level (Haley RW and Dietschy JM, 2004). As the increased amount of cholesterol in body leads to the accumulation of amyloid beta deposits. This is characterized by an increase in inflammatory response and oxidative stress. This risk of the development of AD increases with decrease in tolerance of body towards glucose and increase in resistance to insulin (Chevrier G et al, 2014). The only limitation is the time consumption associated with this model.

TABLE 2: Non Transgenic Models used for Pathogenesis for AD.

Non transgenic models	Natural models	Rats, dogs and various non-human primates are used	Variation can be seen in different models based on the appearance of pathophysiological characteristics.	(Solà C et al, 1993), (Beck M et al), (Chen Y et al, 2014)
	High fat diet induced model	Linkb\w hyper-cholesterolemia and AD is generated.	Other characteristics related to AD can't be seen	(Haley RW and Dietschy JM, 2004), (Chevrier G et al, 2014)

In-vitro Models

Various tissues were cultured in the culture media to depict the features associated with AD. The most commonly used tissue was the brain in which the hippocampus is most important. Initially, the hippocampal neurons were extracted and cultured in the media. Then they were made prone to the amyloid beta peptides which under observation proved to be neurotoxic to neurons of hippocampus. Other trial was made with the brain slices cultured in the media. They were treated with okadaic fragments thus inhibiting the activity of phosphatase enzyme resulting in the appearance of hyperphosphorylated tau protein (Gong CX et al, 2001). They serve to be the great models by linking the connection between neuronal and glial activity.

Cell Models

Stem cell techniques gives a great urge to work on the cultured stem cell lines for the development of drug discovery. The pluripotent stem cell lines are chosen associated with AD and these are cultured to

carry out the testing of the various drugs for the treatment (Yagi T et al, 2011) (Israel MA et al, 2012). Other cell lines which were used were human neuroblastoma cells which clearly depict the amyloidogenic pathway followed during AD (Macias MP et al, 2014). When carnosic acid was made in use to neuro cells associated with amyloid beta fragments, it results in cell apoptosisaggregated by the acid which we use (Meng P et al, 2015). Also, the inhibition adenosine receptors increase the pathological hallmark of the AD like amyloid beta aggregation and the formation of tau protein tau protein hyperphosphorylation leading to the NFT.

TABLE 3: In-Vitro Models used to Demonstrate The Feature Associated With AD.

In-vitro models	Cell models	Pluripotent stem cells Neuroblastoma cells	Similar related to human AD	Lack Aβ and NFT	(Yagi T et al, 2011) (Israel MA et al, 2012)
	Tissue models	Brain slices Cultured tissues	Study at the molecular level	Lack pathological hallmarks of AD	(Gong CX et al, 2001)

CONCLUSION

Great work has been done in the study field of AD with the use of various types of models. The transgenic models serve as an important tool to study the in vivo pathological changes consisting of the amyloid beta senile plaques as well formation of NFT. The in vivo models provide us the role of environment factors which causes the aggravation as well as the progression of AD. They also provide the various target for the treatment of AD by using the novel and therapeutic drugs. Also, the morphology of the plaques was studied containing the amyloid fibrils giving a star shaped appearance. Presence of the microglial cells as well as the astroglial cells and their processes was also observed. The neuritic profiles at different stages of swelling and degeneration in different models like APP, tau, PS1, triple APP\PS1 was studied which suggests that these models are perfect to study the pathogenesis of AD as well as also helpful in designing new strategies for the treatment.

FUTURE PROSPECTIVE

The future prospective deals with the use of genetic technology in the advancement of these experimental models use to us. The microarray and RNA serve as an emerging tool for the development of these models as they allow the more efficient use of the genetic technology in studying the AD. Also, the positron emission tomography (PET) and magnetic resonance imaging (MRI) are the proposed tools in future for studying the brain pathology as well as for the effective diagnostic purpose. Now a day's many studies use machine learning and multivariate analysis methods to differentiate the individuals at different stages of AD. Multivariate techniques are basically used as they establish relationship between variables and are also accompanies with the chance of classification errors. In MRI techniques we usually compare the imaging of normal cognitive with the person with AD. In the future these techniques are surely going to enhance the diagnostic criteria for the AD and will also be helpful in establishing new strategies for the treatment of the disease.

CONFLICTS OF INTERESTS

Authors do not have any conflicts of interests.

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