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Modeling Amyloid Diseases in Fruit Fly *Drosophila Melanogaster*

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1. Introduction

Amyloidoses are a heterogeneous group of diverse etiology diseases. They are characterized by an endogenous production of abnormal proteins called amyloid proteins, which are not hydrosoluble, form depots in various organs and cause functional dysfunctions [Westermark et al., 2007]. Despite of their different structures, these proteins are probably generated by a common pathological pathway. Twenty-seven such proteins have been identified as amyloid precursors in humans [Sipe et al., 2010]. However, the question how and why these proteins form aggregates and cause disease is not still completely clear. A wide range of common neurodegenerative diseases is associated with amyloidosis such as Alzheimer's disease and Creutzfeldt-Jakob disease, as well as non-neuropathic diseases, such as senile systemic amyloidosis and type II diabetes. At present, there is not an effective treatment to prevent these amyloid diseases.

To understand the pathogenesis and to develop novel therapeutic strategies, it is crucial to generate animal models of amyloid diseases in genetically tractable organisms. During the last decades, the genetically amenable fruit fly *Drosophila melanogaster* was established as a valuable model system for the study of variety of human neurodegenerative disorders including Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and familial amyloidotic polyneuropathy [Bilen & Bonini., 2005; Lu & Vogel., 2009]. The advantages of using the *Drosophila* model are that flies have a short lifespan, small size, large number of individuals and simplicity in genetic manipulation [Hirth, 2010]. In addition, *Drosophila* represents a useful model for screening and testing chemical compounds. Moreover, *Drosophila* is an ideal model for screening genetic modifiers of pathogenic process due to their potential to prevent or ameliorate the disease [Marsh & Thompson., 2006].

In this review we will summarize recent progress in developing of fly models for amyloid disease. We address the following issues: (1) creating models of human amyloidosis in *Drosophila* (Alzheimer' disease, prion disease, senile systemic amyloidosis, familial amyloidotic polyneuropathy) and (2) screening of chemical and peptide compounds, as well as modifier genes of protein toxicity in the fly model.

2. Advantages in using *Drosophila melanogaster* to model amyloid diseases

One of the most interesting approaches to research of genetic forms of human diseases is their modeling on fruit fly *Drosophila melanogaster*. For these purposes two basic experimental approaches are used: an expression in *Drosophila* of human genes playing the role in development of diseases, and studying of own genes of *Drosophila*, orthologs of human genes involved in development of diseases [Bier, 2005]. The recent sequencing of the human and *Drosophila* genome has shown that more than 50% of genes of *Drosophila melanogaster* have homologs in humans, and at the same time not less than 60%-70% of genes of human hereditary diseases have the *Drosophila* counteracts [Fortini, 2000; Reiter, 2001]. Therefore, when acting with various models of diseases on *Drosophila* direct research of mutant protein can characterize substantially its participation in a pathogenesis of human disease. Moreover, use of transgenic technology allows to create the strains carrying the human genes and to use them for modulation of concrete physiological mechanisms. On the other hand, genetic experiments with gene knockout can be a basis for definition of unknown cellular protein functions involved in the development of pathological process.

Well-established techniques on the *Drosophila* [Rubin & Spradling, 1982] allows receiving transgenic flies not only according to the certain gene, but also to define an expression of this gene in tissues at various stages of an ontogenesis of the *Drosophila*, due to binary system UAS-GAL4 [Brand & Perrimon, 1993]. The system imported from yeast consists of two independent strains one of which carries an investigated gene under promoter UAS control (Upstream Activating Sequence), and the second strain contains its transcription activator – transcription factor GAL4. For the induction of transgenic expression, UAS strain is crossed to the strain expressing GAL4 under control of the endogenous or specially designed promoter that leads to the expression of investigated gene in tissues where GAL4 expresses. Hundreds of different activator-expressing strains have been generated by the Drosophila community and are available to other investigators.

Temperature- sensitive character of transgenic expression in UAS-GAL4 system has been used for creation of temporal and regional gene expression targeting (TARGET) [McGuire, 2003]. TARGET system is based on ability of yeast protein GAL80 to suppress the GAL4 expression. Joint expression of UAS-GAL4 strain and temperature-sensitive allele $Gal80^{TS}$ [Matsumoto, 1978], under tubulin 1α promoter control leads to the greatest suppression of GAL4 expression at 19°C and synthesis depressions of this protein at 30°C.

The other approach for the direct temporary gene expression by using UAS-GAL4 system is based on creation of hormone-inducible chimeric GAL4 variants: Gal4-estrogen receptor [Han, 2000] and GAL4-progesterone receptor (Gene Switch) [Nicholson, 2008; Osterwalder, 2001; Roman, 2001]. The transgenic expression is controlled with addition of ligands in food of flies or larvae during certain time period that allows excluding deleterious effects of the early expression of transgene. However, it imposes restriction on the use of these approaches on embryonal and pupal development stages [Elliott & Brand, 2008].

The method of insertional mutagenesis has been developed on *Drosophila melanogaster* and became widely used, based on application of mobile genetic elements (ME). ME represent the DNA segments capable to independent transpositions inside the genome. The share of mobile elements in human and mammal genome can reach 40% of the nuclear DNA [Kazazian, 2004]. The quantity of copies of mobile elements from various families changes

from one to several hundreds. ME insertion can essentially change the character of gene expression, and it has become the cause for wide ME application in creation of regulated tissue specific expression vectors [Enerly et al., 2002; Rorth P.,1996; Staudt et al., 2005]. The largest extension in *Drosophila* researches belongs to vectors, framed on the basis of mobile P-element [Adams & Sekelsky, 2002; Bellen et al., 2004]; however property of the P-element to be built in only certain genome sites, limits the mutagenesis in the whole genome. Therefore now approaches with use of other mobile elements preferring insertion sites distinct from the P-element, in particular, *hobo* [Huet et al., 20002; Myrick et al., 2009; Smith et al, 1993] and *Minos* [Metaxakis et al., 2005], are developed.

It is necessary to notice that use of *Drosophila* models allows avoiding such restrictions arising in action with human material, as incomplete family pedigrees, genetic heterogeneity of population, duration of the sampling. At the same time, fundamental aspects of cellular biology, such as regulation of gene expression, membrane transport, cell signaling, synaptogenesis, cellular death, neurotransmitter systems are similar enough in humans and *Drosophila* [Sang & Jackson, 2005].

3. *Drosophila* models of Alzheimer's amyloidosis

Alzheimer's disease (AD) is the most frequent reason of a dementia in elderly and senile age [Davis and Samuels, 1998]. Clinically, AD manifests as a gradual decline of cognitive functions such as learning and memory, which significantly correlates with synaptic loss. The main neuropathological features of AD are well known and characterized by the accumulation of aggregated phosphorylated tau in neurofibrillary tangles (NFTs) and amyloid beta peptide (Aβ) in senile amyloid plaques. Aβ is the peptide with 39 - 42 *amino acid*, a product of the proteolytic processing of the big transmembrane protein which has received a name of **A**myloid **P**recursor **P**rotein (APP). Normally, Aβ in nanomolar quantities is found out in the blood flow and cerebrospinal fluid; however, according to modern representations, accumulation of toxic intermediates of amyloid fibril in AD brain is the central link in all neuropathological processes, including dysfunction of synapses, neurodegeneration, neuron loss and dementia development [De Strooper & Annaert, 2001; Hardy & Selkoe, 2002; Selkoe, 1998]. The appreciable part of works specifies that such intermediates may be soluble oligomers of Aβ [Walh & Selkoe, 2004].

Different membrane proteases known as alpha, beta (BACE) and gamma-secretases, are involved in proteolytic APP processing. The coordinated action of β– and γ-secretases results in the formation of Aβ. γ-secretase represents the protein complex, in which basic component are transmembrane proteins presenilin 1 (PSN1) or presenilin 2 (PSN2) [De Strooper & Annaert, 2000]. All known familial AD forms are caused by mutations in *APP, PSN1, PSN2* genes [Selkoe, 1999]. There are a fly homologue of presenilin genes (*Psn*) [Ye & Fortini, 1998] and homologue of *APP* gene (*Appl*) [Luo et al., 1990] in *Drosophila melanogaster* genome.

Appl is characterized by high degree of homology with APP, it is exposed to similar proteolytic processing, but it lacks the Aβ peptide region and its processing does not lead to neurotoxic effects [Luo et al., 1990; Rosen et al., 1989]. Appl knockout didn't lead to lethal effect, but caused change of behavioral reactions which were restored at APP expression. This indicates functional conservatism between *Drosophila* Appl and human APP[Luo et al., 1992]. Many researches specify the key role of Appl in formation and maintenance of synapses in *Drosophila* [Ashley et al., 2005; Torroja et al., 1996]. Experiments by definition of Appl localization have shown significant Appl enrichment in growing axons and synaptic

structures and participation of Appl in formation and differentiations of synapses in neuromuscular junctions of larvae [Torroja et al., 1996, 1999b]. The overexpression both Appl, and human APP caused disturbance of axon transport [Gunawardena and Goldstein, 2001; Torroja et al., 1999a]. At APP human overexpression in *Drosophila melanogaster* it also was transported in the presynaptic terminal of neurons and postsynaptic sites of neuromuscular junctions [Yagi et al., 2000].

Fly models of human Aβ peptide-induced amyloidosys have been generated employing direct expression Aβ40 and Aβ42, in nervous system in *Drosophila* strains [Iijima-Ando & Iijima, 2010; Moloney et al., 2010]. Interestingly, diffusive amyloid deposits and neuron loss have been detected only in flies carrying the sequence of more amyloidogenic Aβ42 in genome. Amyloid formation was accompanied by progressive age-dependent behavioral defects, and life expectancy reduction. Authors did not detect amyloid accumulation and neuron loss as for flies carrying the sequences of less amyloidogenic $A\beta_{40}$ [Finelli et al, 2004; Iijima et al., 2004]. In other work, flies expressing wild-type $A\beta_{42}$ and Arctic mutant $A\beta_{42}$ (Glu22Gly) showed a decline in climbing behavior, increased intracellular Aβ accumulation and diffuse plaques prior to signs of neurodegeneration [Crowther et al., 2005]. Late findings demonstrated that expression of the Arctic mutant significantly enhanced formation of Aβ oligomers and Aβ deposits, together with a decline of locomotor functions when compared with Aβ-art (artificial mutation L17P) [Iijima et al., 2008].

It has been proposed that dysfunction and loss of synapses underlie in the basis of cognitive disturbances at AD [Hardy & Selkoe, 2002; Honer, 2003 Sze et al., 1997; Selkoe, 2002; Terry et al., 1991]. At the analysis of sporadic AD form it has been established that the significant reduction (> 25 %) of synapse density in a frontal and temporal cortex and in hippocampus was observed already in the early stage of disease [Masliah et al., 1994]. Thus loss of synapses is not age-dependent and it is the specific characteristic of AD [Masliah et al., 2001]. Moreover, the degeneration of only insignificant part of synapses is caused by neuron death whereas the appreciable share of synapses is lost by living cells [Coleman & Yao, 2003].

In addition, transgenic models clearly show that synapse loss strictly correlates with cognitive disturbances and precedes formation of neurofibrillary tangles (NFTs) and amyloid deposits [Duyckaerts et al., 2008; Mucke et al., 2000; Oddo et al., 2003]. Now the most researchers suggest that accumulation of soluble toxic Aβ oligomers in neurons lead directly to degeneration of synapses and the neuron loss [Walsh & Selkoe, 2004]. This suggestion, considerably, is based on the data showing correlation between concentration of soluble non-aggregated Aβ in extracts of cortex and hippocampus, reduction of synapses quantity and degree of cognitive disturbances [Lue et al., 1999]. In summary, despite appreciable number of modeling experiments on the transgenic animals [Haass and Selkoe, 2007; LaFerla et al., 2007; Wirths et al., 2004] it is extremely difficult to prove a hypothesis about casuative the role of toxic Aβ oligomer in synaptic dysfunction *in vivo*. Surprisingly, different $A\beta_{42}$ aggregates had distinctive roles in modulation of synaptic functions. While exogenously prepared small $A\beta_{42}$ oligomers or Aβ oligomers secreted from neurons lead to a reduction of neurotransmitter release; larger-sized aggregates, possibly fibrils secreted by muscle cells, enhanced neurotransmitter release and synaptic transmission [Chiang et al., 2009].

The $A\beta_{42}$ expression induced depletion of mitochondria in axons and dendrites and their accumulated in the somata without severe mitochondrial damage or neurodegeneration [Iijima-Ando et al., 2009]. In addition, significant depletion of presynaptic mitochondria occurred before changes in synaptic transmission [Zhao et al., 2010].

Greeve et al. (2004) have taken an alternative approach to generating flies with Aβ deposition. Because BACE activity is very low or not present in *Drosophila* [Carmine-Simmen et al., 2009; Fossgreen et al., 1998;], overexpression of human APP does not lead to secretion of Aβ leading to the interpretation that all phenotypic effects in these transgenic flies should be attributed to the presence of human APP. When human BACE and APP were expressed in combination in fly eyes Aβ was secreted and diffuse amyloid plaques and age-dependent neurodegeneration of photoreceptor cells were observed. The neurodegeneration phenotype was enhanced in the flies expressing dPsn carrying early-onset familial AD mutations. Surprisingly, neurodegeneration was even more pronounced in APP transgenic flies than in APP/BACE double transgenic flies [Greeve et al., 2004]. Our data confirm these results. We did not find differences in age-dependent neurodegeneration in transgenic flies expressing full size APP with BACE or without BACE. However, transgenic expressing APP and BACE had lower levels of the presynaptic protein GFP- synaptobrevin or GFP-synaptotagmin than transgenic expressing APP alone [Sarantseva et al., 2009a, 2009b]. These findings raise the question whether the decline of synaptic proteins levels and/or neurodegeneration are caused by different mechanisms. Alternatively, we suggest that Aβ reflects just a part of a larger pathological process and independently contributes to different neuropathological abnormalities caused by APP overexpression.

3.1 Screening for genetic modifiers

Drosophila represents one of classical tools used to conduct genetic modifiers screens. The main goal of these screens is to identify proteins or pathways that modulate pathological process. One of the most interesting examples is discovery of modifiers of Aβ pathology. Flies expressing $A\beta_{42}$ in retina have been used for detection of Aβ phenotype-modifying mutations in *Drosophila* genome. These flies developed so-called «rough eye» phenotype characterized by disorganization of photoreceptor cells and reduction of the eye size [Finelli et al., 2004]. Modifiers (suppressors and enhancers) of rough eye phenotype were identified from screening the collection of nearly 2,000 *Drosophila* strains carrying in genome inserts of EP transposon. The EP transposon has a GAL4 activated promoter and modulates the gene activity depending on site and orientation insertion [Rorth et al., 1998]. All strains of this collection were individually crossed to the flies expressing $A\beta_{42}$. As a result of screening of phenotypes and the subsequent DNA-analysis 23 modifiers gene have been discovered. They included genes participating in various secretory processes, cholesterol homeostasis, the innate immune pathway, control of transcription and chromatin remodeling. Eight mutations change the total Aβ peptide level, but only one mutation resulted in 70 % decrease of total Aβ level. This mutation revealed insertion in regulatory zone of neprilysin 2 (nep2) gene [Cao et al., 2008; Finelli et al., 2004]. Neprilysin is one of major neuropeptidases of brain of mammals [Iwata et al., 2001, 2005]. Interestingly, epidemiological studies suggest that reduction in Neprilysin levels may contribute to the onset and/or progression of late-onset AD [Hersh & Rodgers, 2008].

Several studies show that normal cellular presenilin functions and the nature of abnormalities caused by PSN1 and PSN2 mutations in familial AD are not restricted by participation of these proteins in γ-secretase complex and required the further investigations [Baki et al., 2004; Bentahir et al., 2006; Singh et al., 2001; Saura et al., 2004; Schwarzman et al., 1999]. For understanding presenilin functions the search of genetic modifiers modulating Psn-dependent phenotype in *Drosophila* wings and notum has been conducted. 177 modifiers, included the proteins regulating intracellular calcium signaling, stress response and protein folding, components of signal transduction, apoptotic factors and proteins of the cellular cycle. Notably, 58 modifiers interacted with APP, including those involved in calcium signaling. These results provide strong evidence for a link between presenilins, APP, and calcium homeostasis, and suggest that these may play an important role in AD pathogenesis [van de Hoef et al., 2009].

4. *Drosophila* model for transthyretin-associated amyloidosis

Transthyretin (TTR), plasma protein primarily synthesized in the liver, choroid plexus and in retinal pigment epithelium, is the basic transporter of thyroxine and retinol-binding protein in mammals [Goodman, D., 1987; Woeber & Ingbar, 1968]. Three human diseases are characterized by extracellular transthyretin deposits – Familial Amyloidotic Polyneuropathy (FAP), Familial Amyloidotic Cardiomyopathy (FAC) and Senile Systemic Amyloidosis (SSA). SSA is the most widespread form of transthyretin associated amyloidosis, in which the lesion of heart, brain, and pancreas is observed [Westermark, et al., 1990]. FAP and FAC are hereditary forms caused by mutations in the transthyretin gene. Now it is known more than 100 human genetic TTR variants differing with unique amino-acid replacement, of which the majority is amyloidogenic [Connors et al., 2003]. TTR forms amyloid through a process that is initiated by tetramer destabilization. This process results in accumulation of monomers, which can misfold and aggregate into fibrillar structures [Wiseman et al., 2005]. TTR is involved in Aβ metabolism, the basic component of amyloid deposits in Alzheimer's disease [Liu & Murphy, 2006; Schwarzman, et al., 1994]. Moreover, binding TTR to Aβ prevented Aβ aggregation and formation of an amyloid both *in vitro* and *in vivo* [S.H. Choi et al, 2007; Buxbaum et al, 2008]. Despite the fact that *Drosophila* does not have distinct TTR homolog, the expression of its two clinical forms TTRV30M [Berg, I. et al, 2009] and TTRL55P and mutant form TTR-A [Pokrzywa et al., 2007], with two amino-acid replacements (TTRV14N/V16E) [Olofsson et al., 2001] led to development of the phenotypes partially reminiscent of the human pathology. Expression of TTRV30M in the nervous system resulted in neurodegeneration, reduced lifespan, climbing ability, whereas the expression of wild type TTR (TTRwt) showed a milder phenotype. Congo red staining of the *Drosophila* brain shows positive amyloid binding in aged TTRV30M flies [Berg, I. et al, 2009]. Similar results have been received at TTRL55P and TTR-A expression: shortened lifespan, locomotive dysfunction, including flight ability [Pokrzywa et al., 2007]. Notably, that the expression of all three TTR forms (TTRL55P, TTR-A and TTRwt) caused the unusual "dragged-wing" phenotype.TTR aggregates possessed different toxicity. So, the most toxic were TTR aggregations separated from hemolymph and fat body of aged TTR-A flies [Pokrzywa et al., 2010].

Drosophila strains expressing TTR can address specific questions in transthyretin biology. For instance, a variety of TTR-binding partners have been identified over the years [Liz et al., 2009]. However, the biological significance of these interactions remains obscure. Use of

a tractable genetic system such as *Drosophila* can play a key role for the elucidation of cellular pathways and compartments in which these interactions take place.

5. Modeling prion diseases in *Drospohila*

Prion diseases (transmissible spongiform encephalopaties) are an unusual group of fatal neurodegenerative disease including Gerstmann–Sträussler–Scheinker (GSS) syndrome, familial fatal insomnia (FFI), Creutzfeldt–Jakob disease (CJD) and kuru in human and also scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, chronic wasting disease in mule deer and elk, [Prusiner, 1998, Prusiner & Hsiao,1994]. These diseases may present with sporadic, inherited or infectious origins and lead to dementia, motor dysfunction and death [Aguzzi et al., 2008]. The majority of prion diseases cases in humans are classified as sporadic forms and about 10-15 % are the inherited form caused by mutations in *PRNP* gene. Now it is described more than 30 mutations in *PRNP* gene [Mead, 2006]. According to modern considerations, the central pathogenetic event in prion diseases is the conformational conversion of the normal cellular isoform of prion protein (PrP^{C}) into its pathological scarpie isoform (PrP^{Sc}) [Prusiner, 1998]. The precise structural differences between the two PrP isoforms remain to be defined, although it is clear that PrP^{Sc} contains significantly more β-sheet and is more protease-resistant regions. The deposition of PrP^{Sc} in the brain is associated with cerebral damage, including spongiform degeneration and neuronal loss. However, increasing evidence argues against the neurotoxicity of PrP^{Sc}. Significant pathology and/or clinical dysfunction develop with little accumulation of PrP^{Sc} [Flechsig et al., 2000; Manson et al., 1999] and some familial prion diseases are not transmissible, and are not accompanied by the accumulation of protease resistant PrP [Brown et al., 1994; Rodríguez-Martínez et al, 2010; Tateishi & Kitamoto, 1995; Zou et al, 2010]. Thus, it is not clear whether specific conformers are associated with neuronal dysfunction and degeneration [Solomon et al., 2010].

The first attempts to create the model of prion diseases on *Drosophila* were unsuccessful. PrP Syrian hamster (SHaPrP) expression under heat shock promoter Hsp70 did not lead to neuropathology and accumulation of protease-resistent SHaPrP forms [Raeber et al.,1995]. The expression of wild type of the mouse (MoPrP) and human CJD-associated PrP (PG14) [Krasemann et al., 1995] using GAL4-UAS has not also revealed clinical and pathological abnormalities in the flies. Surprisingly, the flies seemed to accumulate very little mutant PrP in the brain compared with the eyes, suggesting that *Drosophila* brain possesses a specific and saturable mechanism that suppresses the accumulation of PG14 [Deleault et al., 2003].

The successes in modeling of prion disease in *Drosophila* was achieved in the expression of wild type mouse prion protein and GSS syndrome-associated mouse prion protein ($MoPrP^{P101L}$) in cholinergic and dopaminergic neurons. The $MoPrP^{P101L}$ flies showed severe locomotor dysfunction, decreased lifespan and neuronal vacuolization associated to age-dependent accumulation of misfolded PrP molecules and intracellular PrP aggregates [Gavin et al, 2006]. In addition, $MoPrP^{P101L}$ induced altered synaptic architectures in larval neuromuscular junctions and progressive reduction of a synaptic scaffolding protein, Discs large (DLG), in adult brains [J.K. Choi et al., 2010]. Flies expressing wild type prion protein displayed no phenotype [J.K. Choi et al., 2010; Gavin et al, 2006].

Expression of wild type PrP (SHaPrP) in *Drosophila* neurons caused lifespan reduction, locomotive abnormality and spongiform degeneration of brain neurons. This was a first

successful attempt on creation of the sporadic form of prion diseases in *Drosophila*. Notably, PrP underwent conformational changes comparable to those of PrP^{Sc}, however flies did not accumulate proteinase K-resistant PrP, indicating that wild type PrP can induce spongiform degeneration in the absence of its prototypical PrP^{Sc} conformation [Fernandez-Funez et al., 2009].

6. *Drosophila* as a model system for discovery of therapeutic compounds for brain delivery

A major obstacle in the treatment of diseases of the central nervous system is the limited penetration of drugs into the brain. A basic reason for low efficacy of many systemically administered therapeutics is insufficient drug delivery due to the presence of the blood-brain barrier (BBB) [Pardridge, 2005]. The BBB is formed by the complex tight junctions between the endothelial cells of the brain capillaries and their low endocytic activity. This results in capillary walls that behave as a continuous lipid bilayer that prevents the passage of polar and lipid-insoluble substances into the brain [Ballabh et al., 2004; Huber et al., 2001; Reese and Karnovsky, 1967]. The BBB also limits the delivery of protein and peptide-based therapeutics that are highly potent, lack toxicity and may prove extremely efficacious for the treatment of many neurological disorders [Laskowitz et al., 2006].

Limited numbers of investigations of brain delivery of therapeutic compounds described in literature are partially due to the difficulties in evaluating and predicting simultaneously the fate of a compound in a therapeutic intervention and the efficiency with which it crosses the BBB. Current methods such as *in vitro* measurements in cell cultures are insufficient to address problem in modeling of CNS diseases. At the same time present models of neurological diseases using rodents often have serious limitations for repetitive testing of a large number of structural variants of drugs. Therefore, to avoid these difficulties we examined the utility of *Drosophila* and its BBB for neuropharmacological research. Recent studies showing structural and functional similarities between the BBB of *Drosophila* the mammalian BBB suggest that *Drosophila* represents a reasonable model for testing the penetration of drugs and peptide vectors into the CNS [Daneman and Barres, 2005; Genova & Fehon, 2003; Schwabe et al., 2005; Stork et al., 2008; Wu et al., 2004]. We have demonstrated the ability of penetratin (protein transduction domain vector) [Derossi et al., 1994] to carry a cargo (apoE mimetics) across the *Drosophila* BBB into brain cells. These apoE mimetics are peptides derived from the receptor binding region of apoE that mimic the functional anti-inflammatory and neuroprotective effects of the intact apoE protein [Laskowitz et al., 2007; Wang et al., 2007]. Amazingly, penetratin fused with apoE mimetics restored cognitive functions in transgenic *Drosophila*. Moreover, penetratin fused with peptide SH8 (inhibitor of Aβ amyloidosis) [Schwarzman et al., 2005] decreased size of Aβ deposits after abdominal injection in *Drosophila* lines secreting Aβ [Sarantseva et al., 2009a]. These results suggest that *Drosophila* may be a very fruitful model system for the development of CNS drugs and studying drug delivery into the brain.

7. Conclusion

Transgenic *Drosophila* lines reproduce many key signs of Alzheimer's disease, prion diseases, FAP, FAC, SSA. Here it should be noted that although experiments with transgenic *Drosophila* do not faithfully recapitulate all aspects of studied amyloid diseases,

they offer real opportunities for studying disease-related pathology. In particular, these models help to explain the contributions of APP and Aβ in familial AD pathogenesis. In general, fly models should be surveyed as the sensitive genetic system, which gives possibility to reveal the cellular processes involved in a pathogenesis of diseases, modifiers of these processes. In a very practical view *Drosophila* strains may be also used to test new therapeutic compounds, which would help resolve a variety of fundamental questions. The discovery of genetic modifiers in *Drosophila* will help to reveal the corresponding human genes and therefore new therapeutic targets.

8. Acknowledgment

This study is supported by the Russian Foundation for Basic Research and by the Program of the Presidium of the Russian Academy of Sciences ''Fundamental Sciences for Medicine''.

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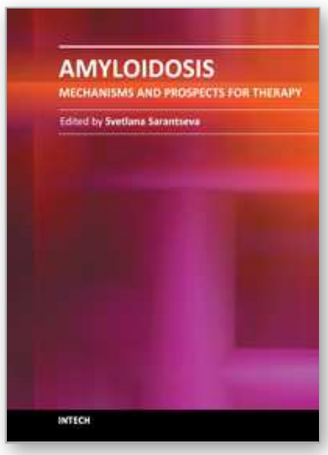

Amyloidosis - Mechanisms and Prospects for Therapy
Edited by Dr. Svetlana Sarantseva

ISBN 978-953-307-253-1
Hard cover, 216 pages
Publisher InTech
Published online 22, September, 2011
Published in print edition September, 2011

Amyloidoses are a heterogeneous group of diverse etiology diseases. They are characterized by an endogenous production of abnormal proteins called amyloid proteins, which are not hydrosoluble, form depots in various organs and tissue of animals and humans and cause dysfunctions. Despite many decades of research, the origin of the pathogenesis and the molecular determinants involved in amyloid diseases has remained elusive. At present, there is not an effective treatment to prevent protein misfolding in these amyloid diseases. The aim of this book is to present an overview of different aspects of amyloidoses from basic mechanisms and diagnosis to latest advancements in treatment.

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