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Review Article

ALZHEIMER'S DISEASE. ASPECTS OF PATHOGENESIS AND EXPERIMENTAL THERAPY

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Abstract

The studies based on the amyloid model of Alzheimer's disease discovered some possible mechanisms involved in the pathogenesis of neurodegeneration. A new complex of proteoglycans of embryonic genesis created by Mkrtchyan L., as well as a hypothalamic proline-rich peptide created by Galoyan A., were used as possible therapeutic approaches that can rescue neurons from further degeneration caused by beta amyloid. The content of neuroactive aminoacids' aspartate, glutamate, glycine, taurine and gamma-amino-butyric acid in cerebral cortex, hippocampus and striatum, as well as the content of neurotrophins, insulinlike growth factor 1 and nerve growth factor in different brain areas, thymus, liver, and blood serum of experimental and control animals were studied. The spontaneous alternation test on Y-maze was chosen from various behavioral tests with the aim of studying rats. The elevated plus-maze test was also used for the estimation of amygdale-mediated system responsible for the sense of anxiety.

It was revealed that the concentration of all investigated aminoacids both in cerebral cortex and hippocampus increased under the influence of proteoglycans of embryonic genesis. It was obvious that gradual recovery of cell structure took place in proline-rich peptide injected experimental group. Moreover, it was showed that injections of proline-rich peptide resulted in a considerable increase in the concentration of insulinlike growth factor 1 in all investigated brain structures, mainly, in the neocortex, hippocampus and hypothalamus after the administration of beta amyloid. Increase of growth factors' level and particularly of insulinlike growth factor 1 is evidently an adaptive response of brain neurons to damage, which is accompanied by high proliferation of hippocampal adult stem cells.

Keywords: *Alzheimer's disease, neurodegeneration, neogenesis, proline-rich peptide.*

Abbreviations: ***GABA*** *– gamma-amino-butyric acid,* ***PEG*** *– proteoglycans of embryonic genesis,* ***PRP*** *– proline-rich peptide,* ***IGF-1*** *– insulinlike growth factor 1,* ***NGF*** *– nerve growth factor,* ***BrdU*** *– bromdeoxyuridine*

Alzheimer's disease, firstly described by German neuropathologist Alois Alzheimer as early dementia (Dementia Praecox) in 1907, is an age-related neurodegenerative disease characterized by progressive loss of memory and deterioration of cognitive functions. Individuals with the disorder usually experience difficulties in learning, performance speed, memory accuracy and problem solving [*Lazarov O et al., 2010*].

According to the data of the World Alzheimer Report 2015 [*WAR, 2015*] there are almost 900 million people aged 60 years and more all over the world. The number of elderly people living in countries with high level of income will be increased by 56% compared with 138% in countries with upper middle income, 185% – with lower middle income and 239% – with low income according to the prognosis from 2015 to 2050. The expected increase in life expectancy promotes rapid growth in numbers of elderly population and is associated with increased prevalence of chronic diseases like dementia.

There were 46.8 million people with dementia all over the world in 2015. This number will be doubled every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050. These new estimates are 12-13% higher than those made for the World Alzheimer Report 2009. It is necessary to mention that the prevalence of dementia among people aged 60 years and more ranges from 4.6%

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in Central Europe to 8.7% in North Africa and Middle East. All other regional estimates fall between 5.6% and 7.6%. Estimated prevalence of dementia is higher in East Asia and Africa in comparison with the data of 2009. According to the World Bank classification, 58% of all people with dementia live in countries with low or middle income and this proportion will increase to 63% in 2030 and to 68% in 2050.

According to 2015 data, 9.9 million new cases of dementia were estimated all over the world implying one new case every 3.2 seconds. These new estimates are almost 30% higher than the annual number of new cases estimated for 2010 in the World Health Organization report, "Dementia: a public health priority" in 2012 [*WHO and ADI, 2012*].

The regional prevalence of new dementia cases is 4.9 million (49% of the total number) in Asia, 2.5 million (25%) in Europe, 1.7 million (18%) in America and 0.8 million (8%) in Africa.

The incidence of dementia increases exponentially with increasing age, doubles every 6.3 year, at the age group of 60-64 years composing 3.9 per 1000 person, and at the age of 90 and more – to 104.8 per 1000 person.The total costs of dementia's treatment have increased by 35.4% from US$ 604 billion in 2010 to US$ 818 billion in 2015.

Secular trends can't be the same in various regions of the world or even among different population subgroups within one country. The experience with changing rates of cardiovascular disease, obesity, diabetes and cancer shows this clearly. Significant variability of secular trends of following chronic diseases reflects different degrees of progress in improving public health, service access to healthcare and strengthening of health systems and services directed to detection, treatment and control of these diseases.

It should be mentioned, that the results of reliable studies (mostly conducted in countries with high income) are currently too inconsistent to reach firm and generalizable conclusions regarding the underlying trends.

According to the Alzheimer's Disease International's (ADI) recommendations, the risk reduction should be an explicit priority in work led by the World Health Organization with clear linked actions including targets and indicators; the investments for dementia should be scaled up, proportionate to the societal cost of the disease; and these investments should be balanced between prevention, treatment, care and cure. ADI approves the mentioned plan and calls for the continuation with a broader agenda and wider representation from the countries and regions most affected by the ongoing epidemy of dementia. ADI endorses the "call for action" agreed at the World Health Organization Ministerial Conference on "Global action against Dementia" [*WHO, 2015*], which needs to be modified into operationalized plan with clear targets and deliverables both at international and national level.

The important neuropathological hallmarks of Alzheimer's disease include the gradual interneuronal accumulation of neurofibrillary tangles formed as a result of abnormal hyperphosphorylation of cytoskeletal tau-protein, as well as extracellular deposition of amyloid-protein as senile plaques with massive neuronal death [*Selkoe D, 2001*]. These pathologies are evident in vulnerable and specific brain areas; and the hippocampus is one of the earliest to be affected [*Braak H et al., 1993*]. The hippocampus is a human brain structure which lies under the medial temporal lobe. Although there is a lack of consensus relating to terms describing the hippocampus and its adjacent cortex, the term hippocampus or hippocampal formation generally applies to the dentate gyrus, CA1, CA2 and CA3 fields and the subiculum. The structure of the hippocampal circuitry has been traditionally characterized as a unidirectional, trisynaptic excitatory pathway [*Li Y et al., 2009*]. Therefore, the entorhinal cortex provides the main source of input to the hippocampus through connections to dentate gyrus. Information flow proceeds from dentate gyrus to CA3 to CA1. In turn, CA1 projects to the subiculum and sends the hippocampal output back to the deep layers of entorhinal cortex. Behavioral studies have suggested that the hippocampus plays a critical role in learning and memory formation [*Squire L, 1992*], which depends on functional and structural changes occurring in the hippocampus, such as long-term potentiation and synaptic remodeling [*Bliss T, Lorno T, 1973; Matsuzaki M et al., 2004*]. The discovery of neurogenesis process de novo in the adult dentate gyrus has allowed the possibility of a new form of plasticity that could sustain memory processes.

Data accumulation supports the view that promotion of adult hippocampal neurogenesis improves pattern separation and spatial memory [*Sahay A et al., 2011; Stone S et al., 2011*]. In contrast, the reduction of neurogenesis may underlie cognitive impairments associated with age and such diseases as Alzheimer's disease [*Clelland C et al., 2009; Lazarov O et al., 2010*].

Neuroplasticity, also known as brain plasticity, is a general term that describes lasting change in the brain of animal throughout life. The term gained prominence in the latter half of the 20th century, when new research showed the lability of adult brain [*Livingston R, 1966; Rakic P, 2002*]. This notion contrasts with the previous scientific consensus that the brain develops during a critical period in early childhood, and then remains relatively unchangeable [*Pascual-Leone A et al., 2005*]. Neuroplastic changes can occur at small scales, such as physical changes of individual neurons, or at whole-brain scales, such as cortical remapping in response to injury. Behavior, ideation, emotions and environmental stimuli may also cause neuroplastic changes [*Pascual-Leone A et al., 2011*] that can impact on healthy development, learning, memory, recovery processes occurring in response to brain damage.

Neurogenesis, defined as a generation process of new functionally active neurons from precursor cells, was traditionally viewed to occur only during embryonic and perinatal stages in mammals [*Ming G, Song H, 2005*]. Altman's pioneered studies, performed decades ago, provided the first anatomical evidence for the presence of newly generated dentate granule cells in the postnatal rat hippocampus [*Altman J, Das G, 1965*]. Functional integration of new neurons in the adult central nervous system was firstly shown in songbirds [*Paton J, Nottebohm F, 1984*]. Multipotent neural stem cells were later derived from the adult mammalian brain [*Reynolds B, Weiss S, 1992; Richards L et al., 1992*]. The field of adult neurogenesis took off after the introduction of BrdU, a synthetical analog of thymidine [*Kuhn H et al., 1996*], as a result of which demonstrations of life-long continuous neurogenesis were demonstrated in almost all examined mammals, including humans [*Eriksson P et al., 1998*].

Over the last two decades, it has become evident that persistent neurogenesis occurs in two specific brain areas of adult mammals: the subventricular zone of lateral ventricles and the subgranular zone of dentate gyrus [*Lois C, Alvarez-Buylla A, 1994; Kuhn H et al., 1996; Eriksson P et al., 1998; Kornack D, Rakic P, 1999*]. Neurogenesis in other regions of central nervous system is a matter of argument up to now [*Gould E, 2007*]. The newborn neuronal cells originate from adult neural stem cells in germinal zones, which are defined by their ability to self-replicate and differentiate into multiple neural cells, including neurons, astrocytes and oligodendrocytes [*Gage F, 2000*]. Two types of neural stem cells have been identified based on their morphological, proliferative behavioral features and expressing markers, although their origin and identity remain to be undefined [*Alvarez-Buylla A, Lim D, 2004; Ma D et al., 2005*]. Slowly-dividing, radial glia-like progenitors (B cells) of subventricular zone that express GFAP and CD133 have been hypothesized to be the primary neuronal stem cells *in vivo*. They are hypothesized to generate rapidly proliferative Dlx2, Mash1, and EGFR (C cells) transit amplifying cells. The majority of these intermediate progenitors subsequently give rise to DCX^+ PSA-$NCAM^+$ neuroblasts (A cells) that migrate into the olfactory bulb through the rostral migratory stream and differentiate into GABA and dopamine-producing interneurons. In parallel, a population of $GFAP^+$ $Sox2^+$ $Nestin^+$ radial cells (type 1 cells) is found to act as quiescent neuronal stem cells of subgranular zone. They may generate actively self-renewing nonradial progenitors (type 2 cells) expressing Sox2 and Nestin but not GFAP, and type 2 cells in turn give rise to DCX^+ neuroblasts that predominantly differentiate into local glutamatergic dentate granule cells. It was recently found that a subset of type 2 $Sox2^+$ cells has the potential to self-renewal and generates both neurons and astrocytes, indicating a possible reciprocal relationship between type 1 and 2 cells of subgranular zone [*Suh H et al., 2007*]. Many studies are referred to the properties of neural precursor subtypes in the adult central nervous system about the sequential steps of adult neurogenesis, ranging from neural precursor proliferation to synaptic integration of newborn neurons [*Alvarez-Buylla A, Lim D, 2004; Lledo P et al., 2006; Duan X et al., 2008*]. Studies have also started to illustrate the functional impact of new

neurons on the existing neural circuitry and their contributions to brain functions under both normal and disease states [*Deng W et al., 2010*]. These areas of research have been very rewarding as they have not only provided significant answers to many fundamental questions about adult neurogenesis, but also made a broad impact on general principles of stem cell regulation, neuronal development, structural plasticity and mechanisms of disease progression. These studies have also led to a number of controversies, intense debates and conflicting conclusions that need to be independently validated [*Ming G, Song H, 2011*].

The studies on the amyloid model of Alzheimer's disease discovered some possible mechanisms involved in the pathogenesis of neurodegeneration [*Aghajanov M et al., 2014*].

One of the crucial events in the pathogenesis of neurodegenerative disorders linked with dementia of Alzheimer's type is the disturbance in neurotransmission based on progressive deficits of neuromediators that is manifested by marked decrease in cognitive behavior, loss of memory and inability in learning as a result of impairment in synaptic plasticity of neurons. Neuroactive aminoacids, such as glutamate, GABA, taurine, glycine and aspartate, play a significant role in these processes [*Clarke N, Francis P, 2005; Schmitt H, 2005; Yu S et al., 2007*]. Similar to neuromediators, they are basically involved in the processes of excitation and inhibition, a misbalance of which can lead to failure of neural network properties. On the other hand, being active metabolic substrates, they are engaged in different metabolic pathways and shift them. For instance, glutamatergic excitotoxicity is neuronal impairment caused by neuroactive aminoacids, such as glutamate. The output of glutamate from the integrative glutamate/GABA system finally leads to neuronal death. The neurotoxicity of beta amyloid is partially related to the over-activation of glutamatergic transmission and excitotoxicity. Activation of GABA (A) receptors by taurine and muscimol (agonists of the GABA (A) receptor) blocks the neurotoxicity of beta-amyloid in rat hippocampal and cortical neurons [*Paula-Lima A et al., 2005*]. These observations provide further insight of mechanisms, whereby beta amyloid affects synaptic function in the brain and may be relevant in the context of synaptic failure observed in Alzheimer's disease [*Chin J et al., 2007*]. In order to show the final physiological effects of aminoacids in brain, it is necessary to understand their interrelation. There is no doubt that better understanding of cellular and molecular pathomechanisms of Alzheimer's disease is a prerequisite for the development of efficient treatments [*Hinners I et al., 2008*].

Bilateral intraventricular injection of aggregated beta amyloid 25–35 in dosage of 30 *nmol*/rat was used for the creation of Alzheimer's-like neurodegeneration in present study. A new complex of PEG created by Mkrtchyan L., as well as a hypothalamic PRP created by Galoyan A., were used as possible therapeutic approaches that can rescue neurons from further degeneration caused by beta amyloid [*Galoyan A, 2000; Mkrtchyan L, 2010*]. The content of neuroactive aminoacids aspartate, glutamate, glycine, taurine and GABA in cerebral cortex, hippocampus and striatum, as well as the content of neurotrophins, IGF-1 and NGF in different brain areas, thymus, liver, and blood serum of experimental and control animals were studied. The spontaneous alternation behavior on Y-maze was chosen with the aim of studying rats. In order to solve this task, it is necessary to ensure normal associative functioning of brain structures (cerebral cortex, hippocampus, striatum), which are involved in learning and short-term memory formation, as well as normal locomotor activity and factors of sensory and attention [*Hughes R, 2004*], that can be damaged during Alzheimer's disease.

It was revealed that the concentration of all investigated aminoacids both in cerebral cortex and hippocampus increased under the influence of PEG [*Yenkoyan K et al., 2009*]. Both in hippocampus and striatum the concentrations of glutamate and GABA significantly increased. It is considered that the abovementioned increase of aminoacids' level is the result of expressed protective action of PEG in hippocampal and striatal neurons. The propounded hypothesis was proved by obtained data regarding taurine. The results showed a considerable increase in taurine level regarding both to control and amyloid, and these aminoacids were the most sensitive to changes after intraventricular injections of beta amyloid 25–35; its concentration has been increased. The latter can be confirmed by the fact, that taurine appears as a pivotal factor of neuronal damage. The damage of neurons can also be overlapped by the

increase of glycine concentration in these structures in animal group who have received PEG after beta amyloid. Thus, except aspartate, the level of all investigated aminoacids in hippocampus and striatum increased. Inadequate changes were detected in cerebral cortex, excepting the increase in GABA level due to regulatory–protective effect of PEG. Hence, the effect of PEG has nonspecific character which, apparently, is caused by the activation of total (nonspecific) way that leads to the increase of investigated aminoacids in brain.

The results of morphological study revealed that under beta amyloid 25-35 exposure the neurons of all layers of cerebral cortex were swollen and lost their typical multipolarity. Neuronal processes were tortuous, whereas in some neurons they were not revealed at all. The same picture was also observed in the other studied brain regions. The gradual recovery of cell structure was obvious in experimental group of animals injected with PRP [*Yenkoyan K et al., 2011*]. Moreover, it was showed that intramuscular injections of synthetic PRP after intracerebellar administration of beta amyloid into the lateral brain ventricles resulted in a considerable increase in the concentration of IGF-1 in all investigated brain structures, mainly, in neocortex, hippocampus and hypothalamus. However, the tendency of NGF decrease was observed in cortex, hippocampus and hypothalamus under the influence of proline-rich peptide. Electrophysiological and morphological studies of hippocampal neurons show, that treatment with PRP results in survival and further maintenance of cells, which indicates his neuroprotective characteristics.

Therefore, it was concluded that treatment with PRP at amyloid induced neurodegeneration may provide normal functioning of neurons during a relatively long period of time by modulation of neurotrophins' level both in brain and periphery. Moreover, huge efforts were made to find out correlation between the release of growth factors like IGF-1, NGF and adult stem cells maintenance in hippocampus after experimental modeling of Alzheimer's disease [*Yenkoyan K et al., 2014*]. Behavioral studies didn't reveal significant changes of spontaneous alteration in beta amyloid 25-35 operated animals regarding the control group. The improvement of spatial memory was noticed in animals injected with proteoglycans of embryonic genesis. This phenomenon can be explained by the origin of reconstruction responsible for the formation of memory structures depending on remodeling and plausible formation of new neurons.

There were no significant changes in fluorescence intensity of Nestin, Vimentin and BrdU/Wnt double-labeled cells in the hippocampus of rats after the injection of beta amyloid 1-42, but the quantity of Vimentin, Nestin/Vimentin double-labeled cells decreased compared with the control group, which confirms the inhibitory effect of neurodegeneration on neural stem cells' maintenance and survival. On contrary, the expression of BrdU positive cells increased, which suggested that neurodegeneration could play a trigger role in stem-cells proliferation [*Yenkoyan K et al., 2014*]. These findings correspond to changes of growth factors: a significant up-regulation of IGF-1 and slight increase of NGF was observed in hippocampus. Increase in growth factors level and particularly in IGF-1, evidently, is an adaptive response of brain neurons to damage, which is accompanied by high proliferation of hippocampal stem cells.

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