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REVIEW

Alzheimer's Disease: An Exacerbation of Senile Phenoptosis

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Abstract—Alzheimer's disease is characterized by progressive memory loss and cognitive decline accompanied by degeneration of neuronal synapses, massive loss of neurons in the brain, eventually resulting in complete degradation of personality and death. Currently, the cause of the disease is not fully understood, but it is believed that the person's age is the major risk factor for development of Alzheimer's disease. People who have survived after cerebral stroke or traumatic brain injury have substantially increased risk of developing Alzheimer's disease. Social exclusion, low social activity, physical inactivity, poor mental performance, and low level of education are among risk factors for development of this neurodegenerative disease, which is consistent with the concept of phenoptosis (Skulachev, V. P., et al. (1999) *Biochemistry (Moscow)*, **64**, 1418-1426; Skulachev, M. V., and Skulachev, V. P. (2014) *Biochemistry (Moscow)*, **79**, 977-993) stating that rate of aging is related to psychological and social aspects in human behavior. Here we assumed that Alzheimer's disease might be considered as an exacerbation of senile phenoptosis. If so, then development of this disease could be slowed using mitochondria-targeted antioxidants due to the accumulated data demonstrating a link between mitochondrial dysfunction and oxidative stress both with normal aging and Alzheimer's disease.

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ALZHEIMER'S DISEASE AS AN EXACERBATION OF SENILE PHENOPTOSIS

According to current data, the process of "normal aging" is not accompanied by a large loss of neurons [1], and reduction of brain volume is rather mediated by neuronal shrinking, atrophy of their dendrite regions, decreased degree of axonal myelination, reduced number of synapses, and changes occurring in their structure [2-4]. Altogether, all such plastic transformations can result in weakening contacts between cerebral structures and slowing of nerve conduction velocity, which are eventually manifested as deteriorated cognitive abilities [5]. In contrast to normal aging, Alzheimer's disease is accompanied by a progressive pattern of cognitive disorders and synaptic degeneration as well as significant loss of neurons in the brain cortex, cerebellum, and basal cholinergic nuclei [6, 7]. It should be noted that degenerative changes in basal forebrain cholinergic nuclei are also observed during normal aging, but the intensity of their atrophy is much more pronounced in Alzheimer's disease [8]. Massive death of neurons during this neurodegenerative disease causes disintegration of different parts of the brain and fully disturbs its functioning, whereas during "normal aging" disturbed links in the brain can be partially compensated by delocalized activity, i.e. involvement of additional cerebral areas during cognitive activity [9] that can significantly prevent deterioration of cognitive abilities.

It is now assumed that accumulation of β-amyloid (Abeta) and hyperphosphorylated intracellular τ-protein are the main factors triggering cognitive disorders and synaptic degeneration during Alzheimer's disease, later resulting in loss of neurons, induction of mitochondrial injuries, and development of oxidative stress, which are accompanied by imbalanced composition and distribution of extra- and intracellular zinc, copper, and iron ions [10, 11]. Accumulations of hyperphosphorylated τ-protein form neurofibrillar tangles in neurons. Brain structures (hippocampus and entorhinal cortex) related to memory display a clear-cut positive correlation between number of neurofibrillar tangles and severity of dementia [12]. Abeta

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forms extracellular clusters in the brain known as amyloid plaques, and the degree of their expression in neocortex during Alzheimer's disease correlates with atrophy of the basal forebrain cholinergic nuclei [7]. Although neurofibrillar tangles and amyloid plaques are considered as markers of the disease, it should be noted that they might be found in the brain under normal aging [12]. This is why, over recent years, a great deal of attention has been paid not to amyloid plaques, but soluble fibrillar Abeta oligomers shown to clearly correlate with pathology and cognitive dysfunction in Alzheimer's disease [13]. Diagnostic signs of the disease start to appear very slowly and sequentially as if it was developing according to a certain program. Currently, six phases in the development of Alzheimer's disease are: phase 1 characterized by reduced level of Abeta in cerebrospinal fluid; phase 2 characterized by elevated level of τ-protein in cerebrospinal fluid and detection of Abeta in the brain by positron emission tomography; phase 3 characterized by retarded cerebral metabolism detected using fluorodeoxyglucose and positron emission tomography; phase 4 characterized by reduced volume of the brain detected by magnetic resonance imaging accompanied by small cognitive impairment; phase 5 characterized by further progressive reduction of brain volume and deteriorating cognitive impairment. Clinically, patients are diagnosed to develop Alzheimer's disease; phase 6 – a terminal stage requiring providing the patient with specialized care [14]. Thus, impaired cognitive abilities and psychoemotional disorders in human behavior during Alzheimer's disease gradually aggravate, wherein an early phase of the disease usually goes unnoticed. Short-term memory is impaired at the onset of the disease, which is accompanied by difficulties in finding the right words during conversation and understanding of complex and abstract thoughts. Such difficulties become even more evident with disease progression. Often, patients forget recent events and people's names, and they cannot continue to live alone without external attention. At the terminal stage, patients are fully dependent on caregivers, they lose ability to speak and comprehend speech, and are unable to move and eat, and they do not recognize their relatives and acquaintances.

Data from epidemiological studies indicate that the population rate of Alzheimer's disease steadily increases with patients' age and comprise 0.7, 4.6, 16.5, and 18.2% in age groups 60-69, 70-79, 80-89, and ⩾90 [15]. The probability of developing Alzheimer's disease is markedly higher in survivors of cerebral stroke or traumatic brain injury. According to recent data, the probability of developing Alzheimer-like dementia in survivors of traumatic brain injury is elevated 2-4-fold [16]. This is because during serious cerebral injuries the concentration of GGA1 and GGA3 proteins responsible for degradation of lysosomal β-secretase (BACE1) is downregulated in cerebral tissues within the first two days post-trauma resulting in accumulation of BACE1. The latter cleaves a protein precursor of β-amyloid, thereby resulting in accumulation of Abeta. It should be noted that patients with Alzheimer's disease were also shown to have upregulated level of BACE1, which is paralleled with low amounts of GGA1 and GGA3 proteins [17]. Apart from acute diseases, chronic disorders of cerebral circulation significantly contribute to increasing probability of developing Alzheimer's disease.

Poor mental performance and low level of education must be specially emphasized as risk factors for development of Alzheimer's disease. According to Katzman [18], mental activity especially during early age results in formation of additional contacts between neurons, which may subsequently decrease risk of developing Alzheimer's disease. Synaptic contacts between neurons are not only required for functioning in the nervous system, but also for maintaining viability of neurons themselves. It is known that developing brain neurons that do not create a required number of synaptic contacts die. Poor functional capacity of neurons in the aging brain can result in rapid decrease in number of synapses or reduction of their functional activity, which eventually serves as one of the causes of neuronal death.

According to our hypothesis, the rate of aging is determined by a set of circumstances, particularly, psychological and social aspects of human behavior sensed by the brain, which depending on input signals can accelerate or slow the intensity of the aging program [19]. Moreover, there is a correlation between age-related mortality and psychological factors such as loss of emotional support from the neighborhood and understanding that a human being cannot any longer master their own fate. Within the concept of phenoptosis, this implies that a death signal does not emerge nor is it accepted for execution while emotional support is provided [19]. This conclusion is entirely applicable to Alzheimer's disease, as at present social exclusion, low social activity, and physical inactivity are referred to as risk factors for development of this neurodegenerative disease. Thus, if aging is a phenoptosis, then Alzheimer's disease when a patient dies within 8-10 years apparently represents an exacerbation of phenoptosis. There is the impression that due to their brain functions (stroke, trauma), people of little use to the community can be eliminated via acute phenoptosis [20-22]. By definition, phenoptosis is the death of a body that is programmed in its genome [21]. However, for Alzheimer's disease it was reliably shown that only ~10% of cases in people under 60 were related to autosomal dominant mutations in the genome. Almost all patients with Down's syndrome surviving up to 40 years of age develop Alzheimer's disease, which serves as a confirmation that the human genome is involved in its pathogenesis. It seems to be related to the fact that in patients with Down's syndrome chromosome 21 containing the gene encoding the protein precursor of Abeta (APP) is inherited in three copies instead of two copies.

POTENTIAL STRATEGY TO SLOW NEURODEGENERATIVE PROCESSES IN ALZHEIMER'S DISEASE

Intellectual, physical, and social activities significantly reduce risk of developing Alzheimer's disease. However, what should be done in case the disease is already manifested? How can development of this type of phenoptosis be stopped or slowed? It seems that like normal aging, Alzheimer's disease is somehow related to mitochondrial dysfunction and oxidative stress [23]. Persson et al. [24] note a large body of data sufficient for considering oxidative stress as an important pathogenetic factor in development of Alzheimer's disease, and, perhaps, in its triggering, as oxidative injury of brain cells represents the first overt event in manifesting signs of Alzheimer's disease. However, a strategy for applying traditional antioxidants (*n*-acetylcysteine, vitamins D, C, and E, selenium, melatonin, lipoic acid, coenzyme Q10) for treatment of Alzheimer's disease provided uncertain results [24, 25]. It seems this was due to the fact that free radicals are necessary for normal vital activity of cells, and their production or overexpression are strictly localized within certain cell compartments. Routine antioxidants lack targeted activity especially given that to achieve an effect they are often applied in high concentration. Therefore, a question arose about targeted delivery of antioxidants towards mitochondria, which are the major source of free radicals as well as their targets. For this, mitochondria-targeted antioxidants were designed. It turned out that such antioxidants (in particular, SkQ1) can partially or even completely prevent age-related changes in rats, such as reduced visual acuity and motor and exploratory activity, sarcopenia, etc. [26-28], as well as slow accumulation of hyperphosphorylated τ-protein, Abeta, and its precursor APP in the brain [29], which are involved in developing neurodegenerative processes during Alzheimer's disease. At present, the majority of neurophysiologists believe that long-term potentiation underlies cellular mechanisms of memory and learning, whereas inhibition of this process by Abeta is considered as a model of disturbed memory processes in Alzheimer's disease. A prolonged post-tetanic potentiation accounts for upregulated efficacy of synaptic transmission between neurons sustained for a long period after applying high-frequency impact on synaptic transmission. By using a model of long-term potentiation on hippocampal slices, we demonstrated that a single intraperitoneal administration of various types of SkQ (SkQ1, SkQR1, SkQT1) to rats might prevent Abeta-triggered inhibition of prolonged potentiation [30-32]. While examining another mitochondria-targeted antioxidant (MitoQ) containing CoQ10 as the active ingredient rather than plastoquinone in SkQ1 and SkQR1 or thymoquinone in SkQT1 and SkQTR1, it was demonstrated that MitoQ, similarly to SkQ, prevented disturbance of long-term Abeta-induced potentiation and reduced overproduction of mitochondrial reactive oxygen species within hippocampal slices [33], as well as prevented pathological process resembling Alzheimer's disease, in transgenic mice manifested in decline of cognitive abilities, accumulation of Abeta, loss of neuronal synapses, and activation of cerebral caspases [34].

Some authors note that, previously, effects related to aging were considered unchangeable and irreversible, especially processes of reduced cognitive abilities related to aging of the brain. However, it now becomes more evident that nutritional calorie restriction or changed composition of the blood via parabiosis as well as mitochondria-targeted antioxidants might partially counterbalance age-related changes in the body [19, 35]. Thus, the data suggest that mitochondria-targeted antioxidants might slow neurodegenerative processes in the brain occurring not only during normal aging, but in Alzheimer's disease as well.

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