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Mechanisms of Neuron Loss in Alzheimer's Disease

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One of the main elements in the pathogenesis of Alzheimer's disease consists of larger decreases in the numbers of neurons in various parts of the brain than seen in normal ageing. The relevance of studying the pathogenesis of this process arises from the fact that neuron loss starts at the early, preclinical stage of Alzheimer's disease, when amyloid plaques and neurofibrillary tangles (the main morphological signs of the disease) have still not formed; neuron loss correlates with the extent of clinical signs of the disease. Data have now accumulated on the likely pathogenetic mechanisms of neuron loss. The aim of the present literature review was to summarize these data.

Keywords: Alzheimer's disease, neurodegeneration, apoptosis, β-amyloid, postnatal neurogenesis.

Alzheimer's disease is a chronic neurodegenerative disease apparent as impairments to memory, thinking, spatial orientation, and speech, along with disorders of the emotional domain. The disease generally starts at ages of more than 60 years, has an irreversible, progressive course, and in its late stages is characterized by amnesia, agnosia, apraxia, aphasia, complete degradation of personality, and loss of self-care ability; it ends with the patient's death from loss of regulation of vital functions or infectious complications. In Russia, Alzheimer's disease affects more than 1.2 million people – 4.5% of those aged more than 60 years [2, 4].

One of the basic elements in the pathogenesis of Alzheimer's disease consists of more intense decreases in the numbers of neurons in various areas of the brain than seen in normal aging [30, 40]. Neuron loss starts at the early, preclinical stage of Alzheimer's disease, when amyloid plaques and neurofibrillary tangles (the main morphological manifestations of the disease) have not yet formed [45, 103]. During this time, there are decreases in the numbers of neurons in hippocampal field CA1, the dentate fascia, the subiculum, and layer 2 of the entorhinal cortex [16, 45, 101, 113]. The process then spreads to the temporal (superior temporal gyrus), frontal, and parietal (supramarginal gyrus) lobes of the cortex [30]. At the late stages of the disease, the process of neuron loss affects the whole brain, including the olfactory bulbs [120], the amygdala [66, 124], the basal nucleus of Meynert [13, 131, 132], the substantia nigra [137], the locus ceruleus [21, 128], and the dorsal raphe nucleus [85].

Decreases in the number of neurons, particularly in hippocampal field CA1 and the entorhinal cortex, correlate with the severity of memory impairments [44]. The likely reason for this is loss of the capacity for rearrangement of the neuronal organization of cerebral structures and addition of new neurons to them, which are required for normal learning processes to take place [9, 32, 47, 112, 134].

These points make studies of the pathogenetic mechanisms of neuron loss in Alzheimer's disease very relevant. Further studies require summaries of the data thus far accumulated. This is the aim of the present review.

The Normal Dynamics of Neuron Numbers in the Brain during Ontogeny

In Alzheimer's disease, the decrease in neuron numbers evidently occurs as a result of impairments to the normal processes maintaining them: postnatal neurogenesis and natural neuron death. We will describe these here.

Neurogenesis is the process whereby new neurons appear in the brain as a result of neural stem cell division and subsequent proliferation and differentiation of daughter

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cells and their functional integration into defined brain structures [5]. This process only occurs at a high level during prenatal development. By birth, neurogenesis terminates in most brain structures and neuron counts reach a stable level, which persists to middle age [96, 99]. During this time, the number of neurons in the adult human brain is, according to different sources, 85–200 billion [15, 93, 133]. Of these, 12–20 billion neurons are in the telencephalon (most in the neocortex, about 20–30 million in the hippocampus, 4.5–7 million in the subiculum, and 10 million in the amygdala), 70–130 billion in the cerebellum, and fewer than one billion in the brainstem and spinal cord [12, 15, 113, 124, 133].

In contrast to other brain structures, the appearance of new neurons in the ventromedial zone of the prefrontal cortex, the dentate gyrus, and the striatum continues after birth in humans (postnatal neurogenesis). The daughters of neural stem cells in the subventricular zone migrate to the prefrontal cortex and striatum, where they become interneurons [107]. We note that another hypothesis holds that new striatal neurons are derived from astrocytes in this brain structure [36, 77]. In the dentate gyrus, new granular neurons appear as a result of the division of stem cells in the subgranular zone [65]. The incorporation of new neurons into the olfactory bulbs in adult humans is dubious (in contrast to other animal species) [18].

In those brain structures in which postnatal neurogenesis is observed, neuron numbers are determined by the dynamic equilibrium between the appearance of new neurons and their natural death. For example, the intensity of neuron replacement in the human dentate gyrus is 0.004% of the population per day, while the proportion of neurons replaced over the whole life is 35% [117].

With age, the intensity of postnatal neurogenesis in the dentate gyrus and subventricular zones in humans (and other mammals) decreases; quickly in the first months of life and then gradually [36, 46, 67, 117]. The inclusion of new neurons into the prefrontal cortex ceases during the first year of life [107]. In the dentate gyrus, postnatal neurogenesis, gradually weakening, continues to old age [67].

Another process influencing the numbers of neurons in the brain is naturally occurring neuron death [76, 91]. Neurons in various stages of maturity undergo naturally occurring death. Some 50% of immature neurons appearing as a result of prenatal and postnatal neurogenesis are not integrated into brain structures and undergo natural termination of their existence [118]. Naturally occurring death is not characteristic of mature neurons, as these cells have well developed mechanisms suppressing it [68].

The main mechanism of naturally occurring neuronal death is apoptosis. Autophagy, pyroptosis, and oncosis are significantly rarer [91, 118, 138]. The intensity of naturally occurring neuronal death can increase with age. Thus, the mouse hypothalamus shows age-related increases in the proportion of apoptotic neurosecretory cells [1].

Naturally occurring neuronal death leads to age-related decreases in the numbers of neurons and their density per unit tissue volume in the hippocampal formation, neocortex, thalamus, and cerebellum [30, 103].

The process of age-related decreases in neuron numbers and densities occurs most intensely in the hippocampal formation, affecting the subiculum and field CA1. By the end of life, neuron death in these structures amounts to 50% of the initial number of cells and the rate of death reaches 3.6% for each 10 years of life [86, 113, 130]. Published data suggest that the natural decrease in the number of neurons in the subiculum and field CA1 terminates after 60 years. In studies demonstrating this reduction, the lower limit of the age range was significantly below 60 years, while studies on the over-60 contingent did not see this pattern [101].

The number of neurons in the neocortex decreases in old age by 10% of the initial number (by an average of one neuron per second), mainly because of the postcentral gyrus, the frontal associative cortex, the anterior zone of the cingulate gyrus, the temporal associative cortex, the inferior parietal gyrus, and the occipital lobe [30, 95, 96]. However, the decrease in the number of neurons in the neocortex was small and some authors have not detected it at all [88, 121].

Mechanisms of Decreases in Neurogenesis and Maturation of Neurons in Alzheimer's Disease

Decreases in neuron numbers in Alzheimer's disease arise from impairment to both of the processes maintaining it: postnatal neurogenesis and naturally occurring neuronal death.

Impairments to postnatal neurogenesis. Changes in postnatal neurogenesis are different in different parts of the brain. The subventricular zone shows decreases, while the subgranular zone of the dentate gyrus shows increases. In addition, new neurons appear where this does not usually occur – in field CA1. These conclusions are based on data showing changes in the intensity of the expression of the molecular markers of neural precursor cells [6] in the brains of dead patients [61, 142]. However, some investigators have suggested that increased neurogenesis in the subgranular zone is more apparent than real, as increased expression of the molecular markers of neurogenesis is linked with increases in glial and vascular rather than neuronal proliferation [20]. Modeling of Alzheimer's disease in animals has demonstrated: increased neurogenesis in the subgranular zone was seen only at the late stages of the disease; at the earlier stages, weakening of neurogenesis occurs in both progenitor cell division zones and at all steps in cell division, including the step forming mature neurons [27, 105].

The literature contains only fragmentary data on the mechanisms weakening neurogenesis in Alzheimer's disease.

Decreases in allopregnanolone have been suggested to be significant, this substance being able to simulate neuronal proliferation via GABA receptors [26, 57, 126]. A decrease in the allopregnanolone level have been seen in the frontal cortex of patients [80]. Studies in a transgenic model

of Alzheimer's disease in mice showed that an increased allopregnanolone level restores impaired cognitive functions [127]. The likely cause of the decrease in allopregnanolone in patients is deranged cholesterol metabolism.

Another suggested cause for the weakening of neurogenesis is cholinergic denervation of the hippocampus and neocortex. Dysfunction of the basal cholinergic system of the brain is one of the main elements in the pathogenesis of Alzheimer's disease. Accumulation of soluble β-amyloid oligomers in brain tissue leads to decreased secretion and increased reuptake of acetylcholine by neurons of the basal cholinergic system, along with degeneration of the axons of these neurons [7]. Experimental weakening of the activity of the basal cholinergic system leads to decreases in the level of neurogenesis in the olfactory bulbs and dentate gyrus of these animals [31].

At the cellular-molecular level, the mechanism of the decrease in neurogenesis in the presence of β-amyloid includes dysregulation of calcium homeostasis and activation of calpains and caspases [51].

Impairment to neuron maturation. The maturation of neurons formed during neurogenesis in the dentate gyrus is impaired in Alzheimer's disease [75]. Neuron processes are unable to develop into axons (neuronal polarization), to lengthen, or to undergo functional integration. These processes are prevented by high levels of glycogen synthase kinase 3β (GSK3β) activity, which are seen in neurons in Alzheimer's disease and are due to increases in extracellular levels of soluble β-amyloid oligomers [7, 74, 98].

Neuron polarization can only occur at low levels of GSK3β in cells [42, 60, 111, 136]. High GSK3β activity impairs the stability and remodeling of neuron microtubules, thus preventing neuronal polarization [55, 115]. The pathogenesis of impaired neuron maturation in Alzheimer's disease may involve three mechanisms of GSK3β action on microtubule remodeling.

Firstly, GSK3β phosphorylates tau protein [59, 70]. Hyperphosphorylation of tau protein is one of the main elements in the pathogenesis of Alzheimer's disease, leading to the formation and accumulation of neurofibrillary tangles in patients' cerebral neurons. Hyperphosphorylated tau protein in neurofibrillary tangles [104] is believed to be unable to interact with the tubulin in microtubules. These undergo depolymerization and their stability decreases, and this leads to impairments to neuron maturation [62].

Secondly, increased GSK3β activity corresponds to inactivation (phosphorylation) of collapsin response mediator protein 2 (CRMP-2) [29, 60, 136]. Inactivation of CRMP-2 decreases its binding to tubulin in microtubules, impairing their polymerization and, thus, axon growth and branching [41, 136].

Thirdly, GSK3β phosphorylates adenomatous polyposis coli protein (APC). This has the result that the interaction of APC with microtubules decreases and their stability is reduced [143].

Increases in the probability of neuron death in Alzheimer's disease. The cellular-molecular mechanism of neuron death in the brain in Alzheimer's disease has not been firmly established. Results from studies of post mortem neuron structure showed that the main mechanism of death was apoptosis. This conclusion was based on the morphological and biochemical changes seen in these neurons. Patients' brains show increases in the number of neurons with signs of DNA fragmentation and forming autophagic vacuoles [114, 135]. However, several researchers have shown that the canonical signal pathways for apoptosis are not the main ones operating. Apoptosis in its canonical version is a quite rapid process, and if it were the main mechanism of death, then neurons showing signs of apoptosis would be significantly less frequent than is in fact the case [141]. On this basis it can be suggested that neuron death in Alzheimer's disease involves nonstandard signal pathways, inducing the same morphological changes in neurons as apoptosis. In addition, the role of programmed forms of necrosis (necroptosis, aponecrosis) have been studied [37].

Pathways increasing the calcium concentration in the neuron cytoplasm. The central component initiating the cellular-molecular mechanisms of neuron death in Alzheimer's disease is an increase in the cytoplasmic calcium concentration [8, 119]. The sources of calcium are the extracellular space and the endoplasmic reticulum (ER).

Increases in the calcium flux from the extracellular space can occur via several pathways. One is the formation of ion channels in neuron membranes by β-amyloid molecules, with passage of calcium ions through these into the neuron cytoplasm (see Fig. 1, *A*) [14, 35, 102]. Another pathway is via the action of soluble β-amyloid oligomers on α7 N-cholinoreceptors [52]. This interaction, direct or indirect, evokes functional activity of α7 N-cholinoreceptors and a calcium ion current through their channels [34, 71, 84]. The mechanism of excitotoxicity may also take part in the increases in neuronal calcium ion concentration. Animal experiments have shown that increased extracellular soluble β-amyloid oligomer levels lead to hyperpolarization of astrocyte membranes, with decreased glutamate reuptake and intracellular accumulation by these cells. An excess extracellular glutamate level leads to extreme excitation of neuron glutamate receptors, increased entry of calcium ions through them, and triggering of pathological intracellular mechanisms [50].

Release of calcium ions from the endoplasmic reticulum results from stress (tension) on the endoplasmic reticulum (see Fig. 1, *B*) [3, 19]. The cause of stress is the accumulation of protein molecules with impaired secondary and tertiary structure (misfolded proteins) in the ER, i.e., β-amyloid and hyperphosphorylated tau protein. The source of intracellular β-amyloid in cerebral neurons remains to be firmly established. Two sources for β-amyloid accumulation have been considered: production within the neuron itself (see Fig. 1, *C*) and internalization of β-amyloid secreted into the intracellular space by other cells (see Fig. 1, *D*).

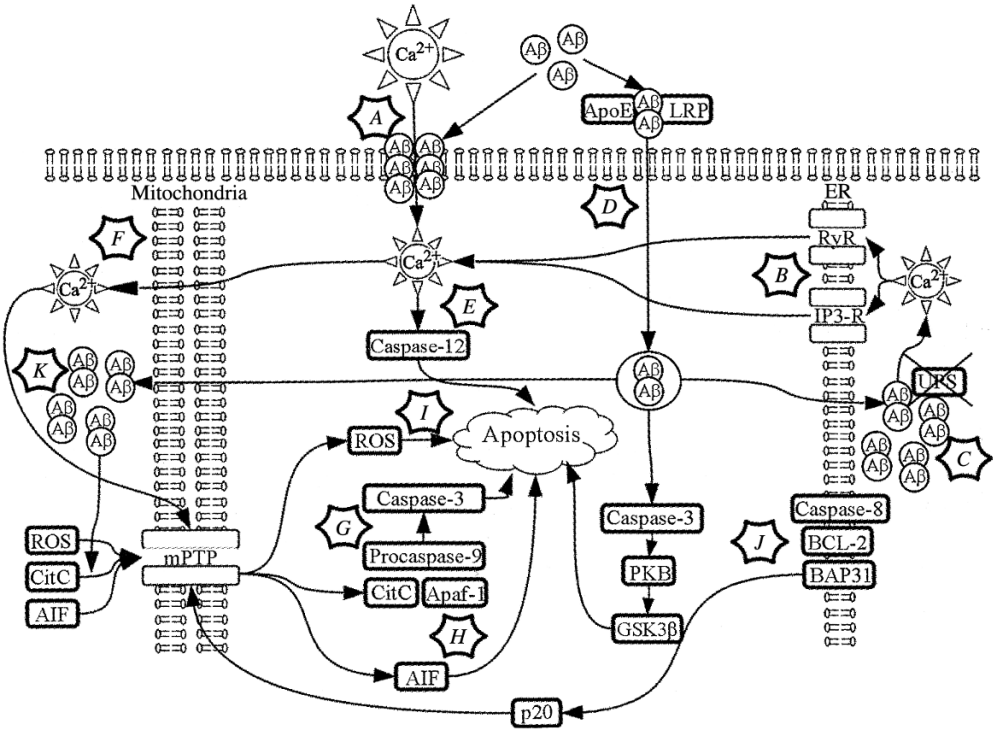

Fig. 1. Hypothetical pathways for neuron death in Alzheimer's disease. Aβ – β-amyloid; Ca^{2+} – calcium ions; ApoE – apolipoprotein E; LRP1 – low density lipoprotein; ER – endoplasmic reticulum; RyR – ryanodine receptors; IP3-R – inositol triphosphate receptors; ROS – reactive oxygen species; CitC – cytochrome c; AIF – apoptosis-inducing factor; Apaf-1 – apoptosis protease-activating factor; p20 – active fragments of BAP31; BAP31 – B-cell receptor-associated protein; BCL-2 – B-cell lymphoma protein; PKB – protein kinase B; GSK3β – glycogen synthase kinase 3β; UPS – unfolded protein response system; mPTP – mitochondrial permeability transition pores. Neuron death in Alzheimer's disease is due to accumulation of calcium ions in the cytoplasm. Sources of calcium accumulation are the intercellular space (*A*) and endoplasmic reticulum (*B*). Calcium release from the endoplasmic reticulum is induced by stress of the endoplasmic reticulum due to accumulation of β-amyloid molecules with unfolded structure within it. These molecules are produced by the endoplasmic reticulum itself (*C*) or enter the neuron from the extracellular space (*D*). Accumulation of calcium ions in the neuron cytoplasm can activate the classical pathway of apoptosis (*E*). Uptake of calcium ions by mitochondria (*F*) induces mitochondrial dysfunction. Mitochondrial dysfunction can induce apoptosis via several pathways. Cytochrome c released by mitochondria triggers the classical apoptosis pathway via apoptosome formation with Apaf-1 protein and procaspase-9 (*G*). AIF released from mitochondria initiates the caspase-independent apoptosis pathway (*H*). Reactive oxygen species released by mitochondria also initiate apoptosis (*I*). Stress on the neuronal endoplasmic reticulum leads to activation of one of the signal pathways of apoptosis, not associated with calcium accumulation in the cytoplasm (*J*). Mitochondrial dysfunction can be induced by accumulation within them not only of calcium, but also β-amyloid (*K*).

Intracellular β-amyloid accumulation as a result of its production by the dead neurons themselves is a natural phenomenon, as β-amyloid is formed in neuronal endosomes as a result of proteolysis of amyloid precursor protein (APP) [94]. This occurs when APP molecules are not cleaved by α-secretase on the cell surface [33, 97, 125]. β-Amyloid molecules can then be degraded in lysosomes (autophagy), secreted by axons [28, 63] or dendrites [129], or transferred to other organelles (Golgi complex, endoplasmic reticulum, mitochondria). Inadequate degradation of β-amyloid in neurons is due to weakening of the mechanisms of autophagy (a cellular dysfunction currently regarded as a candidate for the key component in the pathogenesis of Alzheimer's disease) [92].

Another source for β-amyloid accumulation in the ER is its internalization (uptake from the extracellular space) (see Fig. 1, *D*) [87]. The dominant view is that internalization of β-amyloid occurs via clathrin-mediated endocytosis on interaction of molecules with LRP1 (low density lipoprotein-related protein 1) receptor (see [87] for review). Interaction of β-amyloid molecules with LRP1 occurs indirectly, via a coreceptor or in complex with apolipoprotein E, for which the LRP1 receptor is also specific. Other internalization hypotheses involve lipid rafts containing ganglioside GM1, α7 N-cholinoreceptors, or receptors for advanced glycation end products (RAGE) [106]. After internalization, β-amyloid is located in neuronal endosomes and lysosomes, where molecules are degraded by proteases or form protease-resistant aggregates which are transferred to the ER and mitochondria.

In normal conditions, protein molecules with abnormal structure present in the ER and mitochondria are destroyed by a special molecular-cellular system, i.e., the UPR (unfolded protein response). In overtension (stress) of the ER, when

the UPR system is ineffective, various signal pathways leading to cell death are activated [19]. Data confirming mobilization of this mechanism in Alzheimer's disease include the presence of incorrectly folded β-amyloid molecules (soluble oligomers of this substance) in the ER, hyperactivation of the neuronal UPR system, and activation of ER stress markers in the brains of dead patients [38, 48, 53]. ER stress leads to activation of several signal pathways for neuronal death. Some of these are initiated by release of calcium ions from the ER via ryanodine and inositol triphosphate receptors [64, 82].

The β-amyloid precursor protein intracellular domain (AICD) is able to potentiate the release of calcium from the ER [69, 89]. Molecules of this substance are released within the neuron in response to γ-secretase at the second stage of cleavage of the β-amyloid precursor protein (APP) molecule. The activation of the amyloidogenic pathway of APP cleavage in Alzheimer's disease unavoidably leads to an increase in AICD production. AICD molecules functioning as a transcription factor activate the expression of the genes for proteins involved in controlling cellular calcium balance. The inositol phosphate signal pathway activated by this process leads to activation of IP3 receptors in the endoplasmic reticulum and increased release of calcium ions through these receptors to the cytoplasm [73].

Pathways of apoptosis initiated by cytoplasmic calcium. Calcium ions activate proteases of the calpain and caspase-12 families, which trigger the classical caspase cascade of the apoptosis reaction (see Fig. 1, *E*) [19]. Involvement of this mechanism in the pathogenesis of Alzheimer's disease has been confirmed by experimental data. β-Amyloid induces release of calcium from the ER [83]. Apoptosis induced by β-amyloid is mediated by caspase-12 [90].

Calcium accumulation in the cytoplasm leads to its uptake by mitochondria (see Fig. 1, *F*). Overload of mitochondria with calcium activates mitochondrial permeability transition pores (mPTP), increasing the permeability of the mitochondrial membrane and the release of proapoptotic factors from mitochondria into the cytoplasm: cytochrome c, apoptosis-inducing factor (AIF), and reactive oxygen species [54].

Cytochrome c interacts with Apaf-1 protein (apoptotic protease-activating factor-1) and procaspase-9 to form molecular complexes, i.e., apoptosomes. The appearance of apoptosomes in the cytoplasm leads to activation of caspase-3 molecules and triggering of the classical apoptosis pathway reaction cascade (see Fig. 1, *G*) [23].

The suggestion that caspases are involved in neuron death in Alzheimer's disease is supported by data showing increases in their expression and activity in those cerebral neurons in patients' brains displaying morphological changes typical of apoptosis. The process of β-amyloid accumulation and activation of the apoptosis signal pathways occur synchronously and are colocated in the brain. This particularly applies to caspases-2, -3, -6, -7, and -8 [11, 43, 81, 100] or caspase-2 (independently of caspase-3) [110, 123].

The interaction of β-amyloid and caspases may form a vicious circle (such situations underlie many pathological states): β-amyloid activates caspases and caspases can increase β-amyloid synthesis by activating β-secretase [122].

An increasingly widely held view is that activation of caspases in Alzheimer's disease is not an element of the process of cell death, but is only associated with functional impairments in neurons [56, 116, 139]. Within the framework of this theory, concepts of the role of the caspase-independent apoptosis pathway in Alzheimer's disease, associated with activation of another product of mitochondrial dysfunction – AIF – has been developed [24, 72]. AIF is a mitochondrial flavoprotein which functions to protect cells against reactive oxygen species [39, 109]. Molecules of the mature form of this substance are produced from a precursor and are located on the internal mitochondrial membrane. Proapoptotic factors, particularly β-amyloid, produce proteolysis (involving calpains) of AIF molecules to form the soluble form of this substance, which enters the neuronal cytoplasm and then the nucleus, where it triggers the process of DNA fragmentation and cell death (see Fig. 1, *H*) [49].

Reactive oxygen species are produced by mitochondrial dysfunction – they induce oxidative stress in neurons (one of the main signs of Alzheimer's disease). It is another proposed cause of the activation of apoptosis signal pathways (Fig. 1, *I*) [10, 22]. In addition, oxidative stress-induced lipid peroxidation of cell membranes is accompanied by release of phosphatidylserine into the cytoplasm, which facilities the association between β-amyloid and the membrane and formation of β-amyloid ionic channels and the entry of calcium into the cell through these channels [8]. Thus, the formation of β-amyloid channels leading through a chain of events to oxidative stress and oxidative stress promoting the formation of β-amyloid cannels operates as a vicious cycle which can theoretically amplify the pathological process in the neuron.

Signal pathways of apoptosis not linked with calcium accumulation in the cytoplasm. The literature contains descriptions of various apoptosis signal pathways able to lead to neuron death in Alzheimer's disease but not linked with calcium accumulation in the cytoplasm.

Application of stress to the endoplasmic reticulum initiates apoptosis not only by release of calcium into the cytoplasm, but also by formation of a complex of integral proteins in the ER membrane: BAP31 (or BCAP31 – B-cell receptor-associated protein 31), BCL2 (C-cell lymphoma protein), and caspase-8 (see Fig. 1, *J*). BAP31 undergoes cleavage in this complex, with release of its p20 fragment. p20, acting on mitochondria, increases their membrane permeability and cytochrome c release [23]. In the cytoplasm, cytochrome c can activate the apoptosis signal pathway described above, forming apoptosomes and caspase-3.

Mitochondrial dysfunction is an obligatory component of neuronal death signal pathways in Alzheimer's disease [17, 140]. It has been suggested that mitochondrial dysfunction in Alzheimer's disease can be elicited not only by

mitochondrial calcium overload, but also the accumulation of structurally damaged β-amyloid molecules within them, coming from the endoplasmic reticulum (see Fig. 1, *K*) [19]. Transport of β-amyloid from the ER into mitochondria probably does not occur over a distance, but within the framework of mitochondrial membrane-associated endoplasmic reticulum [108]. In mitochondria, β-amyloid molecules bind alcohol dehydrogenase molecules, producing impairments to oxidative phosphorylation and ATP synthesis and decreasing membrane potential [25, 79]. The increase in mitochondrial membrane permeability induced by these processes leads to release of cytochrome c, AIF, and reactive oxygen species from mitochondria into the cytoplasm, these being factors triggering the mechanisms of apoptosis described above.

The proapoptotic actions of intracellular β-amyloid may be mediated by glycogen synthase kinase 3β (GSK3β) [78]. If this is so, β-amyloid monomers will inactivate protein kinase B (PKB) via caspase-3; the active form of PKB inactivates GSK3β. The resulting increase in GSK3β activity may lead to mobilization of apoptosis signal pathways [58].

Conclusions

Summarizing published data leads to the conclusion that one element in the pathogenesis of Alzheimer's disease is neuron loss in the brain. In those brain areas in which neuron death is seen in normal aging, this process is more intense in Alzheimer's disease (the precentral and postcentral gyri, parietal and temporal associative areas of the cortex, subiculum, and hippocampal field CA1). In addition, the number of neurons starts to decrease in those brain areas where there is essentially no change in normal aging (the dentate gyrus, entorhinal cortex, olfactory bulbs, basal nucleus of Meynert, amygdala, substantia nigra, locus ceruleus, raphe nuclei). Neuron death starts at the early stages of disease development and is one of the causes of the impairments of brain function seen in this disease. The cause of the decrease in the number of neurons is an increase in the probability that they will die, with suppression of the maturation and functional integration of new neurons in the dentate gyrus, along with weakening of postnatal neurogenesis in the subventricular zone and, according to some data, in the dentate gyrus. The cellular-molecular mechanism of neuron death in Alzheimer's disease has not been established. Neurons show elements of apoptosis, though there are data excluding the operation of its canonical mechanisms. The possibility that other, poorly studied mechanisms of cell death operate is under study. The most likely initiator of neuron death is the intracellular accumulation of β-amyloid induced by dysfunction of the endoplasmic reticulum and mitochondria and leading to activation of intracellular caspase-independent apoptosis pathways.

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