

● PERSPECTIVE

## The brain compensatory mechanisms and Alzheimer's disease progression: a new protective strategy

Compensatory/adaptive mechanisms in the brain are hypothesized to be involved in its protection from the Alzheimer's disease (AD) progression. These mechanisms are activated by malfunctioning of various brain systems: antioxidant, neurotrophic, neurotransmitter, immune, and others. Detailed analysis of compensatory/adaptive capabilities of these systems might be a start point for further discovery and development of perspective approaches for early diagnostics and treatment of AD and associated neurodegenerative disorders.

AD is characterized by memory impairment, dementia, cholinergic neuron loss, amyloid-beta ( $A\beta$ ) peptides deposition forming senile plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein in the brain. This age-associated chronic neurodegenerative pathology is intensively expanding in modern human society and has been noted to start well in advance of its clinical manifestations. The "latent" period in AD progression appears to be associated with involvement of compensatory mechanisms in the brain which are able temporarily or permanently to protect it from the neurodegenerative processes even initiated by specific mutations in the amyloid precursor protein or presenilins. Understanding of principles how these mechanisms work and how manipulate them allows the developing of new approaches in early diagnostics of AD, its effective prophylactic, and therapeutic treatment.

The main efforts in this field were associated with the attempts to characterize an imbalance between the neurodegenerative and regenerative processes in the brain (for review, Iqbal et al., 2014). However, most of conventional approaches are predominantly oriented on a clinical stage of the disease, when the compensatory mechanisms are at a "saturated" stage: either completely exhausted or hyperactivated, which makes them inaccessible to detailed studying. Associated with this, a lack of experimental models directly imitating the progression of AD was the main restrictive factor in the "compensatory" field. In our previous studies, the animals with surgically removed olfactory bulbs (OBX-animals) showed typical behavioral, morphological and biochemical AD hallmarks (Nesterova et al., 2008), and evident disturbances in interrelations between different brain areas (Bobkova et al., 2008). Recently, we have demonstrated in OBX-mice a biphasic time course in the AD hallmarks' expression (in particular, the spatial memory impairment and the  $A\beta$  level rising in the hippocampus) after the bullectomy (Bobkova et al., 2013).

Protective and therapeutic capabilities of these compensatory mechanisms can be released at various levels of the brain functioning.

Surprisingly, the neurofibrillary tangles and  $A\beta$  have been

revealed to be able to display an *antioxidant activity* (Moreira et al., 2008). Furthermore,  $A\beta$ , as a chelator of some metals (cuprum, iron, and zinc), can be involved in normal *neurotrophic functions* in the brain. Commonly, both  $A\beta$  generation and tau-protein phosphorylation are associated with recovery of oxidative homeostasis in the cells. At early stage of AD, activated both micro- and astroglia, accompanying the disease, have been shown to be involved in engulfment of both  $A\beta$  and remains of decayed neurons and, additionally, in prevention of the neurofibrillary tangle maturing. The late stage of AD is characterized by evident imbalance between  $A\beta$  accumulation and its utilization in the brain (Moreira et al., 2008).

At early, but not late, stage of AD progression, the level of *transthyretin*, a protein inhibiting  $A\beta$  aggregation and detoxifying cell-damaging conformers, has been shown to be increased that precludes both  $A\beta$  oligomerization and tau-protein hyperphosphorylation (Buxbaum et al., 2008). A protein, *neprilysin*,  $A\beta$ -degrading endopeptidase, displayed similar AD progression profile in the cerebrospinal fluid (CSF) in AD patients. The compensatory brain mechanisms in these patients seem to be involved in an associative rising of both the level of *clusterin*, a protein associated with the clearance of cellular debris, and the extent of  $A\beta$  utilization after delivery of  $A\beta$  complexes into the neuroglial cells and/or in blood stream.

In OBX-mice, we revealed a close association between memory improvement, morphobiochemical brain markers normalization and enhanced levels of an *endogenous heat shock protein* (HSP70) in the hippocampus (Bobkova et al., 2013). HSP70, as a chaperone, protects neurons from  $A\beta$  aggregation and toxicity whereas its capability to produce very stable complexes with the tau-protein protects them from hyperphosphorylation. Recently, we have shown that a subchronical intranasal injection of HSP70, at a small dose, effectively protected OBX-mice from the memory loss both at early and late stages of AD progression (Bobkova et al., 2014a).

Depleting level of a presynaptic marker, *synaptophysin*, closely associated with lowering of synaptic receptor density in both AD patients, transgenic animals and OBX-mice (Bobkova et al., 2014b), has been shown to be compensated in part by enhancing level of a postsynaptic protein, PSD-95 (Leuba et al., 2008). This protein is well known to be supportive for functioning of the AMPA and NMDA receptors, which are important for memory formation. In our previous study on OBX-mice, a rising of the *serotonergic* (5-HT) receptors density was revealed in the cortex and the hippocampus, that we supposed to be a compensatory reaction on the bullectomy-produced lowering of both neuronal density and 5-HT content in the dorsal *n.raphe*, the main source of serotonin for the frontal brain areas (Gurevich et al., 1993).

In AD patients, the levels of *anti- $A\beta$  antibodies* in the serum and/or CSF may correlate with AD progression, thus, making them potentially useable as a treatment approach and/or the early diagnostic and prognostic markers for the disease (Dorothee et al., 2013). This compensatory reaction is evidently associated with  $A\beta$  elimination from the brain.

However, the immunological approach has been shown to be ineffective in clinics seemingly because of its traditional use at very late stage of the disease, when the compensatory mechanisms were completely unworkable. Moreover, even at early stage of AD progression, this approach needs to be specified for the intercepting of those processes which are exactly associated with depression of compensatory mechanisms. We suggest that the selective immunological blockade of A $\beta$  targets, mediating its neurotoxicity, might be an effective and balanced approach at early stage of AD, allowing the implementing of A $\beta$  beneficial functions in the brain. Given close association between A $\beta$ -produced neurotoxicity and activation of neurotransmitter receptors, we attempted to uncover those of their fragments which contained specific binding sites for A $\beta$ . After immunization with the fragments of extracellular domains of  $\alpha$ 7-subtype either of the acetylcholine or prion receptors, evident improvement in both spatial memory and morphology of cortical and hippocampal neurons, in parallel with the A $\beta$  level lowering, were revealed in OBX-mice (Kamynina et al., 2010; Bobkova et al., 2014b). The antibodies to these fragments had to be noticed to exert obvious protective effects on hippocampal cells culture treated with the A $\beta$ <sub>1-42</sub> oligomers as well (Bobkova et al., 2014b). Recently, we have performed several pilot experiments on OBX-mice with the immunological blockade of p75-neurotrophin receptors, which are well known to be involved in A $\beta$ -induced cytotoxicity. Only immunization with two from nine selected fragments of p75 receptor, and with induction of high level of specific antibodies, showed spatial memory improvement, lowering of A $\beta$  in cortical and hippocampal extracts, and protecting of the forebrain acetylcholine system in OBX-mice (in press). We suggest that understanding of intimate mechanisms of the neurotrophin receptors A $\beta$  binding and use of suitable immunological tools might be one of the most perspective approaches for AD treatment.

It should be mention, however, that this paper does not introduce all aspects of the brain compensatory mechanisms functioning at latent phase of AD, in particular, associated with the controlling of hormonal processes, apoptosis, astrocyte functions, and neurogenesis. Nevertheless, we hope that the main idea about these mechanisms involved in protection from AD progression might be a start point for further discovery and development of perspective approaches, based on the releasing of the endogenous brain reserves, for early diagnostics and treatment of AD and associated neurodegenerative disorders.

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