IN DEPTH REVIEW

Neural network plasticity, BDNF and behavioral interventions in Alzheimer's disease

Hubka P

Institute of Pathological Physiology, Faculty of Medicine, Comenius University, Bratislava, Slovakia.
peter.hubka@fmed.uniba.sk

Abstract

Alzheimer's disease (AD) is characterized by a gradual and hierarchical decline in cognition that is essentially connected with the functional properties of brain areas with the highest degree of plasticity. Corresponding brain regions are mostly affected by histological determinants of AD. Crucial pathways involved in maintaining the neural plasticity were also shown to be impaired in AD. Brain derived neurotrophic factor (BDNF) seems to be one of the crucial factors connected with the majority of cognitive and plasticity deficits observed in AD. Recent studies indeed confirm that BDNF is severely disturbed in AD and form an important signaling pathway influencing neural plasticity and neural network status in general. Recently, several behavioral interventions including physical and mental activity or training programs, environmental factors during the early development, and dietary restriction were shown to enhance BDNF levels, neurogenesis, neural cell survival and plasticity and thus improve cognitive properties of the brain. Described behavioral interventions could form a promising approach for AD prevention and treatment programs for prophylactic purposes or in the early stages of AD *(Ref. 106)*.
Key words: neural network plasticity, brain-derived neurotrophic factor, Alzheimer's disease, exercise, diet.

Alzheimer's disease (AD) is a neural disorder characterized by progressive development of dementia with gradual and hierarchical decline in cognition. Both features are essentially connected with the functional properties of neural networks in the brain areas involved in processing of higher cognitive functions. One of the basic features of these brain areas consists of an adequate degree of adult neural plasticity (1). Indeed, the most affected brain areas are those with the highest degree of adult plasticity. The hippocampus, temporal and parietal cortices are brain areas, which dysfunction is the most severe in AD patients. On the other hand, the primary sensory cortices with a relatively low degree of adult plasticity are resistant to functional deficits. Interestingly, the olfactory bulb function, which is characterized by a very high degree of neural plasticity throughout life, is severely affected in AD patients (2, 3). All described brain areas are phylogeneticaly young, mature very late in the course of ontogeny and retain relatively high degree of adult plasticity (4, 5). All these properties make them susceptible to development of neurodegenerative diseases including AD. One of the two basic histological determinants of AD – neurofibrillary tangles – consists of tau protein, which is involved in synapse reorganization and thus synaptic plasticity (6, 7, 8). Consequently, AD and neural plasticity are very closely connected and understanding complex facets of this relation could be very important for both pathophysiology and therapy of AD.

Neural plasticity

Neural plasticity is a complex dynamic process for maintaining the best adaptation of neural network properties to the changing external environment. Basic modules of neural plasticity comprises an adaptation of intrinsic properties of single neurons, a reorganization of synaptic connections between neurons and incorporating of the new neurons into existing neural network. Although the mechanisms underlying neural plasticity is not yet completely understood it was shown that excitatory/inhibitory balance, neurotrophins, Ca^{2+} dynamics, intracellular and extra-

Institute of Pathological Physiology, Faculty of Medicine, Comenius University, Sasinkova 4, SK-811 08 Bratislava, Slovakia

Address for correspondence: P. Hubka, PhD, Inst of Pathological Physiology, Spitalska 24, SK-813 72 Bratislava 1, Slovakia.
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cellular matrices are important determinants of plastic changes in neural networks (10, 11, 12, 13, 14, 15). Resulting remodeling of the neural networks is a consequence of the balanced interplay between described phenomena.

Neural network reorganization is generally induced by changed pattern of neural activation that locally destabilizes existing brain structures. Such destabilization leads to activation of Hebbian form of plasticity that could change synaptic strength very effectively and rapidly (seconds to minutes) by means of coincidence detection. Synapses that are co-activated are strengthened and desynchronized synapses are weakened (16). This form of plasticity is, however, destabilizing while it operates according to the positive feedback rule (17). The most important synaptic structures involved in Hebbian plasticity are glutamatergic AMPA and NMDA receptors. Homeostatic plasticity represents the other stabilizing and slower (hours to days) form of neural plasticity (17, 18). This form of plasticity comprises adjusting intrinsic excitability of neurons, synaptic scaling (modifying the level of activity on all synapses of the particular neuron to maintain the stable level of its activity) and modulation of the level of Hebbian plasticity in neurons (metaplasticity) (19, 20, 21). Cellular mechanisms involved in neural plasticity/stability machinery include changing in synaptic receptor number and their subunit composition (22, 23, 24, 25), formation, retraction and motility of dendritic spines (26), Ca^{2+} signaling pathways (27), protein formation and degradation (28).

On the systemic level, neural plasticity of the specific cortical regions could be affected by the activity of certain neuromodulatory systems in the brain. Cholinergic, serotonergic, adrenergic and dopamonergic systems seem to be involved in modulating of plasticity level of the cerebral cortex (29, 30). These systems are generally activated by non-specific afferent pathways, which are thought to convey information about the context of the specific information (visual scene, sound etc.) processed in different cortical areas. These systems signal the contextual value of specific signals (relation to previous experience, emotional content etc.) and could play a permissive role for reorganization and then stabilization of the new information (31). Thus, neuromodulatory systems are substantially important for acquiring the new information and its long-term retention, and for adaptation to unfamiliar environment. Both processes crucially determine cognitive abilities of an individual.

A lot of studies revealed that almost all cellular and systemic mechanisms involved in neural plasticity machinery are disturbed in the brain of AD patients. Specifically, Ca^{2+} homeostasis, which is involved in different mechanisms connected with neuronal plasticity including dendritic spine motility, Hebbian as well as homeostatic form of plasticity was found to be impaired in AD (32). Impaired Ca^{2+} homeostasis could also lead to excitotoxic injury and invoke apoptosis in neurons. Balance between inhibition and excitation seems to be maintained even despite the markedly decreased number of synaptic connections (33). Composition of synaptic receptor subunits is, however, changed, which could affect functional properties of synaptic transmission and plasticity (33). It was shown that reelin, a protein that is important in developing neural networks as well as in adult plasticity (34), together with apolipoprotein E signaling pathway contributes to inhibition of tau protein phosphorylation (35). Hyperphosphorylation of tau protein is a crucial step toward formation of paired helical filaments (PHF) found in AD brains (36, 37, 38, 39). Furthermore, it was found that very high degree of synaptic plasticity during hybernation cycle is accompanied by tau phosphorylation and formation of reversible PHF-like structures (40). Hyperphosphorylation of tau protein could be a consequence of impaired plastic changes associated with elevated Ca^{2+} level leading to activation of apoptotic pathways. It was proposed that tau protein hyperphosphorylation could represent a protection against the cell death while neurons expressing phosphorylated tau are more resistant to apoptosis (40, 41).

On systemic level, basal forebrain cholinergic system that critically influences neural plasticity (30) is severely impaired in AD (42, 43). Interestingly, other important neuromodulatory systems (serotonergic, noradrenergic and dopaminergic) seem to be not significantly affected in AD (44).

In AD patients as well as in animal models of AD, cognitive decline was more strongly correlated with the synaptic density decrease than with ß-amyloid plaque or neurofibrillary tangles accumulation (45, 46). In the animal model of AD, synaptic density and cognitive decline was clearly observed while no ß-amyloid plaque depositions were detected (46).

All described cellular or systemic deficits found in AD are connected with mechanisms of neural plasticity. Although important mechanisms of plasticity are severely impaired in AD, several studies have suggested that parallel signaling pathways are activated in order to reduce disbalance in neural networks activation found in the course of AD progression (33, 47) and cognitive decline is observed later than pathological findings are (48). These facts should be taken into account for therapeutic interventions in AD patients especially in early stages of the disease. Early identification of AD development is crucial while protective interventions against rapid AD progression in the early stage of the disease could be mostly affective.

Brain-derived neurotrophic factor (BDNF)

BDNF is a neurotrophin with the most widespread expression in the developing and adult mammalian brains (49), acting mainly through high-affinity trk B receptor. BDNF is important for survival of many types of neurons as well as for neurogenesis in adult brain (50, 51). During the last decade, a lot of evidence was collected to show that BDNF is critically connected with the neural plasticity through its important influence on neural responsiveness, synaptic morphology, transmmiter release, balance of excitation and inhibition (52, 53, 54). Deficits in BDNF-TrkB signaling complex is related to deficits in neural circuits and their plasticity and hence deficits in learning, memory and overall cognition (50, 56, 57).

Downregulation of BDNF was found to be associated with many brain-related disorders (58, 59, 60). Disturbances in BDNF activity were recently found also in AD (61, 62, 63, 64, 65). In

AD, brain structures are not equally affected by reduced BDNF protein content. It was reported that brain regions mostly impaired in AD have corresponding deficits in BDNF signaling. Specifically, hippocampus, frontal, temporal, parietal and entorhinal cortices are mostly affected by reduced BDNF protein content and Trk B receptor distribution (64). Interestingly, no significant difference in BDNF immunoreactivity was reported between neurons containing and neurons free from neurofibrillary tangles (66). Strongly reduced BDNF reactivity was found in core region of ß-amyloid plaques while surrounding neurons express strong BDNF immunoreactivity (66). Interestingly, absence of BDNF and Trk B protein content was found in astrocytes and microglia of AD patients (67).

The central role of BDNF in development of AD is further supported by findings that almost all pharmacological therapy currently used in AD is, usually unintentionally, connected with upregulation of BDNF signaling pathways (65). BDNF levels was shown to be increased after drugs interacting with glutamatergic system through NMDA or AMPA receptors (68, 69, 70), canabinoids (71), GABA-B antagonist (65, 72), estrogens (73), phosphodiesterase inhibitors (74), and lithium (75).

Taking together, impairment in BDNF signaling pathway is substantially disturbed in AD but only in certain brain areas. Direct exogenous increase of the BDNF level should be considered with cautious while exogenous administration of BDNF would increase overall level of BDNF even in regions containing normal BDNF levels. Abnormal increase in BDNF level could invoke undesirable effects on neural networks in affected regions manifesting as seizure or epileptic-like activity (59, 76). As a consequence, too high and too long excitatory activation could induce metabolic disbalance leading to the activation of apoptotic pathways in brain areas, which are not affected by AD. Such interventions could thus even worsen the deficits in the brain of AD patients.

Behavioral interventions aimed to stabilize neural networks

AD as many other brain related disorders is caused by mixture of genetic predisposition and environmental factors. In the recent years, several studies provide evidence that susceptibility to AD could be decreased by certain life style factors. Specifically, physical and mental activity and diet at middle-age positively influence incidence of AD (77, 78, 79). Epidemiological studies that investigate differences in the incidence of AD between rural and urban populations and between populations of different cultural background have found substantial differences between studied groups indicating that life style factors are indeed important for pathophysiology of AD . Underlying systemic, cellular and molecular pathways that could explain such results are not known. Recent studies have, however, revealed several plausible mechanisms involved in protection against AD development. Interestingly, almost all mechanisms comprise maintenance of neural plasticity degree and BDNF level in neural tissue.

It was clearly shown that animals reared in enriched environment perform better in cognitive tasks and their cortical and hippocampal BDNF level was upregulated in comparison to their standardly reared mates (82, 83). Enhanced physical activity was also shown to increase BDNF levels and cognitive performance (84, 85, 86). It was suggested that exercise is an effective antioxidant therapy (87). Physical and mental activity thus seems to desirably interact with AD development. Indeed, recent studies proved that environmental enrichment and voluntary exercise caused marked reduction of ß-amyloid deposits in a transgenic model of Alzheimer's disease (88, 89) and synaptic activity affects ß-amyloid production (90). Furthermore, behavioral plasticity-based training programs are able to significantly enhance cognitive functions in older adults with non-pathological age-related cognitive decline (91). We could thus expect that similar plasticity reinforcement programs could be useful also in patients with AD.

Environmental influence during the early stages of development (during maturation) could also be very important for the susceptibility neurodegenerative diseases. Maternal care affects the BDNF level, cholinergic innervation in hippocampus and enhances spatial learning and memory in rats (92). On the other hand, psychological insult in early development was shown to influence susceptibility to several degenerative brain disorders (93).

Most dietary approaches with respect to AD were focused on the dietary composition. Vitamin E and C (used separately or in combination) seem to be effective in AD, probably through their antioxidative properties (94, 95, 96), but their effects are still contradictory (97). Recently, dietary restriction, especially intermittent fasting, was shown to be protective to neural tissue, cardiovascular system and against tumorigenesis (98, 99, 100). Increased levels of BDNF and increased neurogenesis in hippocampus and cerebral cortex were shown to be associated with dietary restriction (101, 102, 103). Furthermore, preconditioning induced by dietary restriction decreases apoptosis and inflammatory response in cardiac tissue (100). While apoptosis and inflammation are present in brain tissue of AD patients (104), it is reasonable to expect similar benefits of dietary intervention before the onset or even in the early stages of AD.

All mentioned behavioral interventions (physical and mental activity, environmental factors during the early development, dietary restriction) were proposed to invoke adaptive cellular response via synthesis of BDNF, heat-shock protein 70 and glucose-regulated protein 78. These factors are involved in mechanisms of cellular protection against oxidative and metabolic injuries (105), promotes neurogenesis and neural plasticity (106) that could protect neural tissues against development of AD or reduce the AD progression.

Concluding remarks

Neural plasticity seems to be severely defected in AD and its deficits are responsible for cognitive decline observed in AD patients. BDNF is crucially disturbed in AD and form an important signaling pathway influencing neural plasticity and neural network status in general. Proper reinforcing of the important

signaling pathways could be promising approach for therapeutic interventions in AD patients especially in early stages of the disease. Physical and mental activity, environmental factors during the early development, and dietary restriction are causative and very promising approach for AD prevention and treatment programs for prophylactic purposes or in the early stages of AD.

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