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Role of interneurons and neural circuit dysfunction in Alzheimer's disease

Role interneuronů a dysfunkce nervových okruhů u Alzheimerovy nemoci

Bachelor´s thesis

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Prohlášení:

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Abstract

Alzheimer's disease is one of the most common neurodegenerative disorder that results in altered network activity, in particular cognitive decline. Majority people with AD experience memory impairment, poor judgment, disorientation and learning difficulties. Several hypotheses try to explain the cause of the disease, but it's poorly understood. Due to the fact that changes in brain structure arise years before clinical symptoms emerge, the available therapeutic treatments can only reduce the impact of neurodegeneration, but not to reverse. Interneurons, as a part of neural circuits, play an important role in the formation of cognitive abilities. Most of interneurons in CNS are inhibitory and they effectively control the network synchrony. Network hypersynchrony is an increased synchronization of neural activity and it's linked to AD pathology. Dysfunction of interneurons is resulted in altered network activity in patients with AD.

Keywords: AD, brain, rat, interneurons, hypersynchrony.

Abstrakt

Alzheimerova choroba je jednou z nejrozšířenějších neurodegenerativních poruch ve svetě, které vedou ke změně aktivity nervových a neuronových okruhů, zejména ke zhoršení kognitivní funkce. Většina lidí s AD trpí poruchou paměti, špatným úsudkem, dezorientaci a problémy s učením. Několik hypotéz se snaží vysvětlit příčinu nemoci, ale není to zcela pochopeno. Vzhledem k tomu, že změny v mozkové struktuře vznikají roky před vznikem klinických příznaků, dostupná terapeutická léčba může pouze snížit dopad neurodegenerace, nikoliv však zvrátit. Interneurony, jež jsou součástí neuronových okruhů, hrají důležitou roli ve formaci kognitivních schopností. Interneurony v CNS jsou většinou inhibiční a efektivně řídí synchronizaci neurálních sítí. Síťová hypersynchronie je zvýšená synchronizace nervové aktivity a je spojena s patologií AD. Dysfunkce interneuronů má za následek změnu síťové aktivity u pacientů s AD.

Klíčová slova: AD, mozek, potkan, interneurony, hypersynchronie.

List of used abbreviations

Aβ: β-amyloid peptide
Ach: acetylcholine
AD: Alzheimer's disease
ALCOVE: The Alzheimer Cooperative Valuation in Europe
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
APOE4: apolipoprotein ε4
APP: β-amyloid precursor protein
APs: action potentials
BDNF: brain-derived neurotrophic factor
CA: Cornu Ammonis
CNS: central nervous system
CPC: clinic-pathological correlation
CSF: cerebrospinal fluid
DMN: default mode network
DG: dentate gyrus
EOAD: early-onset Alzheimer's disease
EEG: electroencephalography
FAD: familiar AD
Fd: fascia dentata
FDG-PET: fluorodeoxyglucose positron emission tomography
LOAD: late onset Alzheimer's disease
LTD: long-term depression
LTP: long-term potentiation
MRI: magnetic resonance imaging
mGluRs: metabotropic glutamate receptors
MAP: microtubule associated protein
NFTs: neurofibrillary tangles
NMDA: N-methyl-D-aspartate
NP: neuritic plaques
NREM: non-rapid eye movement
NT: neuropil threads
O-LM: oriens-lacunosum moleculare
PHF: paired helical filaments
Pre: external principal stratum
Pri: internal principal stratum
PS1: presenilin-1
PS2: presenilin-2
PV: parvalbumin-expressing interneurons
ROS: reactive oxygen species
REM: rapid eye movement
SSP: somatostatin-positive
trans-ACPD (3R-aminocyclopentane dicarboxylate)
VDCCs: voltage-dependent Ca^{2+} channels

Contents

Introduction

Alzheimer's disease is a progressive and irreversible disorder that worsens over time. The symptoms that signal the onset of the dementia are short-term memory loss, difficulties in solving the problems, losing track of time and other early signs of disease. At the last stage of AD patients lose control on physical functions and need round-the-clock assistance with daily activities. This thesis will describe some anatomical aspects of the disease; in particular, what brain areas are mainly affected and what brain cells are impaired in AD. It is also important to understand the alterations of neural oscillatory activity, especially damage of gamma oscillations. Gamma oscillations are modulated by processes, such as motor and memory tasks encoding, sensory processing, attention and other cognitive mechanisms, that are impaired in AD. Most of interneurons in CNS are inhibitory and they form 20-30% of the neocortex. They control the excitability of principal cells, i.e. pyramidal, granule and Purkinje cells.

The aim of the thesis is to describe role of interneurons and how their dysfunction affects neural circuits and cognitive ability in general.

Alzheimer's disease – an overview

Alzheimer's disease (AD) is the most common type of dementia and accounts for 60 to 80 percent of dementia cases, referring to data from Alzheimer's association (Alzheimer's Disease Facts and Figures, 2018). This disease is ruinous and irreversible, leading to destroyal of the basic components of the human nature, such as learning and memory and daily functioning (Schmid *et al.*, 2016). Multiple cognitive symptoms (memory and thinking), as well as non-cognitive symptoms (emotions and self-control) occur and gradually worsen during the period of years, and also differ among patients with AD. Those patients commonly face memory impairment (Vallet *et al.*, 2016), disorientation (Joray *et al.*, 2004), poor and/or slow judgment (Johnson, Bonilla and Hermann, 1997), and difficulties in language and intellectual disability in general.

Majority of people with AD are 65 and older and are affected by late onset Alzheimer's disease (LOAD), therefore increased age is the highest risk factor. However, the disease can be diagnosed before the age of 65 and then it is called early-onset Alzheimer's disease (EOAD) (Wattmo and Wallin, 2017). The EOAD is almost definitely caused by mutations in the specific genes, while the genetics of LOAD remains unexplained. The other high risk factors include depression and anxiety (Burke *et al.*, 2017), which can also be the symptoms, Apolipoprotein ε4 (APOE4) allele with higher risk for women at younger age (Neu *et al.*, 2017), low education and occupational attainment (Stern *et al.*, 1994), reduced cognitive activity (Wilson *et al.*, 2007), lack of physical exercises (Luchsinger *et al.*, 2009), head trauma(Jellinger, 2004), high alcohol consumption (Heymann *et al.*, 2016), high blood pressure (Shih *et al.*, 2018), type 2 diabetes mellitus (Li, Wang and Xiao, 2016) and many other risk factors yet to be determined.

Nowadays, it is known that changes in brain structures arise years before cognitive decline begins (Beason-Held *et al.*, 2013). In addition, the study shows that no change in personality or behavior was detected before identification of the onset of mild cognitive impairment or dementia (Terracciano *et al.*, 2017). As was recommended by the Alzheimer Cooperative Valuation in Europe (ALCOVE) project, the diagnosis of the dementia should start much earlier than in current practice, and the term "timely diagnosis" reflects this.

The diagnosis of Alzheimer's disease is based on its symptoms and risk factors,

despite that it is complicated to track all of the cognitive symptoms in the disease due to their duration. The method to precisely determine the incidence of AD does not exist yet. For this reason the cooperation of specialists, such as physicians, neurologists and geriatricians, as well as family members and friends is essential. A variety of cognitive tests, various neuroimaging techniques as structural magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography (FDG-PET), and cerebrospinal fluid (CSF) evaluation, have a crucial role in diagnosis of AD (Schmand, Eikelenboom and Van Gool, 2011). In particular, amyloid plaques and neurofibrillary tangles are widely-accepted criteria for AD identification (Castellani, Rolston and Smith, 2011).

AD is one of the most rapidly growing diseases between 50 main causes of global years of life lost between 1990 and 2013, as reported in global statistical data from the Global Burden of Disease Study. Moreover, the number of patients diagnosed with Alzheimer's disease is expected to increase significantly in the coming decades. Population ageing markedly elevates the occurrence of AD and it is of greatest interest to find an effective treatment. There is still no cure for AD, however current researches are intensified on prevention, diagnosis, treatment of AD, and promise to decelerate the exponential growth of the number of patients diagnosed with AD.

Main structures affected by AD

Alzheimer's disease is very diverse clinic-pathological condition. The neurodegenerative lesions multiply during the relatively long period of time, while the disease progresses until its terminal phase. Moreover, patients with this disorder, especially early-onset AD, generally tend to survive into more advanced stage (Perl, 2010). For the definitive diagnosis of AD autopsy is needed, and the specimens of the brain acquired from such a terminal phase of the disease frequently show a large burden of AD lesions (Perl, 2010). Those pathological changes discovered in post-mortem brains not always represent the clinic-pathological correlation (CPC). Therefore, the elucidation of the sequence of the neuropathogenic events leading to progression of the disorder is complicated.

Those facts all together brought on the speculation about staging of the Alzheimer's disease. In particular, how the earliest stage of the disease may be distinguished from other stages and other types of dementias and disorders, since the dementia in general can appear as a result of more than one pathological process (NIA, 1997). Some brain regions are more susceptible to the neuropathological changes than the others, see later (Braak and Braak, 1991)(Braak and Braak, 1993). This could help researchers to orient towards studying of phenomena that could underlie these changes.

1. Brain areas (MRI, anatomy, neuropathology)

The model of specific AD-associated lesions will better understandable after explanation of some fundamental anatomic facts. The specific neuropathological changes can appear in numerous cortical and subcortical regions.

Cortical regions

The principal characteristic of human brain is evolutionary expanded cerebral cortex, and it is the area where Alzheimer's disease begins (Braak and Braak, 1993). The cerebral cortex includes neocortical (isocortical) and allocortical areas (Braak, 1980).

1. 1. Allocortex

In comparison to neocortex, allocortex is a very small part of cerebral cortex and is comprised of the hippocampal formation (1), the entorhinal region (2) and the presubiculum (3) (Braak, 1980).

1) Hippocampal formation encompasses the dentate gyrus (DG, fascia dentata), the Cornu Ammonis (CA, Ammon's horns) and the subiculum (Braak, 1980). The term "Hippocampus proper" is usually used to define the dentate gyrus together with the Ammon's horns. Being a well-developed structure of the gray matter tissue in the medial temporal lobe of the brain, C-shaped hippocampal formation is elevating from the floor of the inferior horn of each lateral ventricle, extending approximately from the level of the amygdala up to the posterior end of the callosal commissure, the splenium (Braak, 1980).

The fascia dentata is a grey matter made of the three distinct layers, i.e. the molecular layer (the outermost), the granular and the polymorph layer (Amaral, Scharfman and Lavenex, 2007). The molecular layer contains relatively few cells, while the granular layer consist of the small densely-packed "granule" cells, which are dominant in the whole dentate gyrus (Amaral, Scharfman and Lavenex, 2007). The granule cells project the unmyelinated axons called mossy fibres to synapses on the dendrites of the polymorphic layer and of the CA3 pyramidal cells (Amaral, Scharfman and Lavenex, 2007). In addition, the polymorph layer and the CA4 (which is also called „the hilar region" or „hilus") do not have clear differences in their anatomical structure (Lorente De Nó, R. 1934).

The Cornu Ammonis is the area between the DG and the subiculum. It is subdivided into four different areas: CA1, CA2, CA3, and CA4. The fourth sector of Ammon's horn is not divided to the layers, and, as was mentioned above, can be considered as a part of the dentate gyrus. It is dominated by the modified pyramidal cells without systematic organization (Braak, 1980). In contrast to CA4, CA3 is composed of systematically arranged pyramids. These cells have the long microdendrites which receive input from the mossy fibers of the granule cells (Braak, 1980). CA2 is a small-sized region that comprises superficial and profound lamina of pyrimidal cells (Braak, 1980). The pyramids of the first sector (also called Sommer's sector) are subdivided again into two layers, the superficial and profound lamina, and the cells have relatively long distance from each other (Braak, 1980).

The subiculum can be found between the Ammon's horn and the presubiculum, consisting of large specialized pyramidal cells (Braak, 1980). It has synapse contact with the first sector of Cornu Ammonis and entorhinal cortex, and it is considered the head hippocampal output.

2) In the human brain the entorhinal region spreads over both the gyrus ambiens and anterior parts of the parahippocampal gyrus (Braak, 1980). This area is located in the caudal end of the temporal lobe and can be considered as a main boardline between the hippocampus and the neocortex. The rhinal sulcus detaches the anterior lateral border, while the posterior is detached by the collateral sulcus (Braak and Braak, 1995). The human entorhinal cortex can be distinguished by its rich laminar differentiation, and the differences in the pattern of those layers is used to divide the region into smaller subunits. The laminae is made up of external principal stratum (Pre) and internal principal stratum (Pri), lamina dissecans and broad molecular layer (Braak, 1980). The main layers of the entorhinal cortex also consist of three separated layers (Pre-α, β, γ and Pri-α, β, γ). Pre-α is considered to be the most remarkable layer due to its cellular islands or lines of large and medium-sized nerve cells. Layer Pre-β comes after Pre – α and it dominantly consists of slender pyramidal, triangular and spindle-shaped cells of small size. Those cell bodies form a thin apical non-branched dendrite, which pierces an overlying Pre-α. Layer Pre-γ can be described as a cell-sparse zone predominated by the slender spindel-shaped or pyramidal cells. Pri-α layer, which is primarily composed of pyramidal cells, is situated directly below the lamina dissecans. The cells of the lamina are enriched by a pigment. Consimilar to a Pre-β lamina, Pri-β also has the small slender pyramidal cells as a main component of the layer, and those cells form a thin apical dendrite. The nerve cells of the Pri-γ lamina show distinctive shape of cell bodies and characteristics of dendrites.

The transentorhinal region is another remarkable area of the human brain. This subregion is forming a circumference of the entorhinal cortex and abuts on the temporal proisocortex (Braak, 1980). It goes between the temporal proisocortex and isocortex. The significant characteristic of the transentorhinal cortex is the gradual descent of the layer Pre-α (Braak and Braak, 1995).

3) The presubiculum is the part of allocrtex which includes the proper presubicular subregion, the parasubicular subregion, transsubicular subregion (Braak, 1980). It is relatively easily differentiated from the subiculum as it has one external cell layer of small pyramidal cells (Ding, 2013). The presubiculum on the sides abuts on the subiculum and on the entorhinal cortex (Braak, 1980). The presubiculum is thought to be an important region coding the spatial information

(Rolls, 2006), however the anatomical and physiological considerations are still unspecified.

1. 2. Isocortex

The isocortex (or neocortex) is the largest part of cerebral cortex in human brain. Together with the allocortex it comprises the outer layer of the cerebrum. It has deep ridges (gyri) and grooves (sulci) and this is the reason why it takes most of the area of the cerebral cortex (Chi, Dooling and Gilles, 1977). The neocortex is divided into frontal, parietal, occipital and temporal lobes. In view of its organization and number of horizontal layers (total of six layers), the isocortex can be considered the most advanced expanded region of the cerebrum (Braak, 1980). The layers of the isocortex are marked from the outer layer to the inner, I to VI, differentiated by the type of the neurons and their afferent and efferent connections (Braak, 1980). Those layers are: I, molecular layer (lamina zonalis); II, external granular layer (lamina granularis externa); III, pyramidal layer (lamina pyramidalis); IV, internal granular layer (lamina granularis interna); V, ganglion cell layer (lamina ganglionaris); and VI, spindle cell layer (lamina multiformis) (Brodmann and Garey, 2006). The human isocortex is typically described as composed from the three different vertical areas: 1) the motor areas are responsible for the control of voluntary movements; 2) sensory areas are responsible for the receiving of the perception of the numerous feelings; 3) association areas make up the rest of the cerebral cortex, located outside of the primary (motor and sensory) areas, it combines the motor and sensory signals (Holloway, 1968). There are also defined primary visual (striate) cortex and secondary visual (prestriate) cortex that are parts of the occipital lobe (Braak, 1980).

Subcortical regions

Because Alzheimer related neuropathological changes can also appear in the subcortical regions of the brain, some of those structures will be briefly described below (Braak and Braak, 1991).

The basal ganglia are a group of large subcortical nuclei in the bottom of the forebrain. It is typically divided into two, the corpus striatum and the amygdalar complex (Carpenter, 2011). The corpus striatum (also striate nucleus) is C-shaped structure, comprised from two separated by the white matter tract nuclei, the

caudate and putamen (Telford and Vattoth, 2014). The amygdalar complex is a complex of many subnuclei located deep in the temporal lobe (Amunts *et al.*, 2005). The amygdala is strongly connected (including reciprocal connections) with the hippocampus, the diencephalon, the frontal cortical regions, hypothalamic nuclei, olfactory brain regions, basal ganglia and the brain stem (Nieuwenhuys *et al*. 1988).

The thalamus is a grey matter structure located in the dorsal part of the diencephalon (Telford and Vattoth, 2014). The main part of the thalamus is dorsal thalamus. It is divided into thalamic subnuclei by reason of different anatomical and clinicopathological specifications (Dekaban, 1953). The thalamic nuclei projects out different connections to the cerebral cortex, which defines their functions, and the cortical areas correspond to different thalamic nuclei (Herrero, Barcia and Navarro, 2002).

The hypothalamus is a brain structure located below the thalamus and forming a ventral part of diencephalon (Swaab *et al.*, 1993). There is isomorph area made of invariable cells and heteromorph area of numerous cell types (Lang, 1985). The hypothalamus contains a big amount of nuclei with numerous functions, and those nuclei are connected with many different areas of the human brain (Vallet *et al.*, 2016).

The substantia nigra or "black substance" consist of two nuclei, the pars compacta and the pars reticulata, and it is located in the mesencephalon (Telford and Vattoth, 2014). Its name is due to the fact that some parts of substantia nigra, in particular the pars compacta, are predominated by dopaminergic neurons with high level of neuromelanin (Telford and Vattoth, 2014).

Neuropathology of Alzheimer's disease

Neurodegeneration in AD, which results in brain changes, is specific depending on brain regions, certain layers and even different cell types (Braak and Braak, 1993). Neurodegeneration and especially loss of synapses are the main processes that are fundamental for the increasing cognitive impairment (Terry *et al.*, 1991). The primary noticeable damage related to AD is increasing accumulation of proteins between and within the cells, which typically cannot be detected in the human central nervous system (Heiko Braak and Eva Braak 1993).

The extracellular senile plaques are mainly composed of insoluble deposits of β-amyloid peptide (Aβ) in the grey matter, whereas intraneuronal neurofibrillary tangles (NFTs) are aggregates of abnormally phosphorylated microtubule associated protein (MAP) tau (Bancher *et al.*, 1989), (Kang *et al.*, 1987).

The precursor proteins for Aβ (the β-amyloid precursor protein, APP), presenilin-1 (PS1) and presenilin-2 (PS2) undergo the mutations during progress of AD. The γ-secretase is the final enzyme in the pathway that aggregates the peptide. The catalytic subunit for γ-secretase can be both PS1 and PS2.

The role of MAPs, such as tau, MAP1 and MAP2, is stabilization of microtubule system of the cell by interaction with tubulin followed by tubulin assembly into microtubules. The quantity of tau in normal brain is 2-3 moles phosphate/tau (Khalid Iqbal, Fei Liu, Cheng-Xin Gong 2011). Hyperphosphorylation of tau protein suppresses the native role of tau. In the brain of patients with Alzheimer's disease, the tau was approximately 3 to 4-fold more phosphorylated than the normal adult brain and these hyperphosphorylated structures are polymerized and form the paired helical filaments (PHF), which, in turn, form neurofibrillary tangles.

Staging of Alzheimer's disease

Eva and Heiko Braak in 1991 had published a study, in which they proposed the division of the neuropathological changes of AD into 6 stages (the so-called Braak and Braak stages) with gradually increasing involvement of the brain (Braak and Braak, 1991). They evaluated eighty-three brains of individuals with and without features of dementia obtained at the autopsy.

Depositions of amyloid

Stage A. Mainly in the frontal, occipital and temporal lobe of isocortex is appearing a relatively small amount of amyloid deposits, while hippocampal formation persists without amyloid. Stage B: This stage shows a presence of amyloid in almost all isocortical association areas; the hippocampal formation is involved mildly. Stage C: dense amyloid depositions can be seen in all isocortical areas including core sensory and motor fields; the hippocampal formation remains with same amount of amyloid deposits, as described in the stage B. Several subcortical structures, such as thalamic and hypothalamic nuclei, striatum, are gradually impaired too.

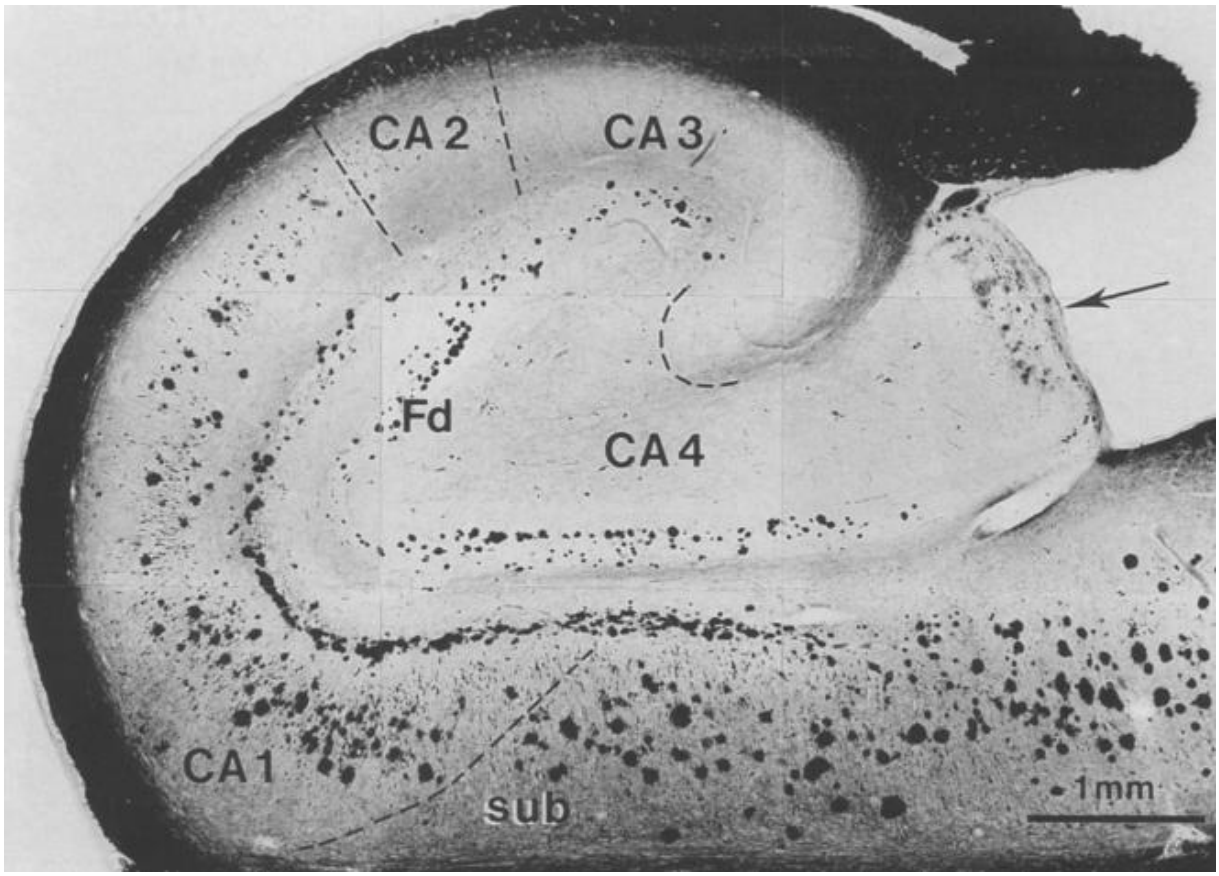

Fig.1. Pattern of amyloid deposits in the hippocampal formation in Stage C. Dotted lines indicate the boundaries of the subiculum (sub) and sectors CA1 (Cornu Ammonis) to CA4. The arrow points to fluffy material accumulated along the free surface of the dentate gyrus (Fd, fascia dentata) (Braak and Braak, 1991).

Neurofibrillary changes

Neurofibrillary changes include NFTs, neuritic plaques (NP) and neuropil threads (NT).

Stage I: the transentorhinal cortex is the first part of cerebral cortex that is being involved. In particular the projection neurons of the transentorhinal cellular layer Pre – α are the first neurons that start to develop neurofibrillary tangles and neuropil threads.

Stage II: the pathology increases in the transentorhinal Pre – α and extends to entorhinal Pre – α. The CA1 region of hippocampus is slightly impaired by NFT too. Stages I and II correspond to transentorhinal involvement.

Stage III: the neurofibrillary changes in both the entorhinal and transentorhinal layers Pre – α get worse and start to damage the neighboring neurocortical association areas. The hippocampal formation still shows only a mild involvement of CA1. The pyramidal cells of the subiculum start to develop NFT on this stage.

Stage IV: the neurofibrillary pathology extends to the medial temporal gyrus. Isocortex shows modest impairments. The number of NFTs in the CA1 of hippocampal formation increases. Subiculum is mildly involved. The Pre-α layer is severely affected. Noticeable damages of the layer Pri-α and Pre-β are present. Stages III and VI correspond to limbic lobe involvement.

Stage V: the number of tangles in the Pre-α increases; Pre-β and even Pre-γ now are severely affected; all regions of hippocampal formation are involved; the neocortical pathology extends and there is a large number of NP in frontal, superolateral and occipital directions, reaching the peristriate region.

Stage VI: on the last stage of the progression of AD all changes are reinforced. Pre-α and Pri-α layers, CA1 region of the hippocampus are characterized by major loss of neurons; most areas of neocortex are severely affected; the pathology reaches primary and secondary neocortical areas. Stages V and VI correspond to isocortical involvement.

2. Brain pathways and circuits (DTI, tractography)

Circuits are functional models that basically create relatively small or large systems of neurons from single cells to ensembles and thus allow processing of nervous activity. The microcircuits of different parts of the brain have similar organization in terms of types of neurotransmitters, short-term and long-term plasticity, synaptic kinetics and synaptic connections (Silberberg *et al.*, 2005).

As I mentioned before, the distinct symptom of Alzheimer's disease is cognitive impairment, such as learning and memory deficit, poor judgment, attention and concentration problems, altered processing speed and psychomotoric tempo. Those cognitive abilities are postulated to be represented by certain neural circuits in the brain and their synaptic plasticity (Paulsen and Sejnowski, 2000). Because the nerve cells are strongly interconnected, the neural circuit dysfunction can be viewed as the consequence of impaired neurons (Zott *et al.*, 2018).

Synaptic plasticity

The plasticity in general is the adaptability of an object to changes of its environment. The synaptic plasticity is the process by which synaptic junctions are able to strengthen or weaken in response to changes of their activity (Hughes, 1958).

Two types of synaptic plasticity can be distinguished on the basis of timescale: short-term plasticity and long-term plasticity. The first one lasts for tens of miliseconds to a few minutes, the second can last even up to few month. The process that represents an increase in synaptic strength is long-term potentiation (LTP); long-term depression (LTD) represents a decrease in synaptic strength (Bear and Malenka, 1994). Cellular mechanisms such as LTP and LTD are considered to underlie learning and memory encoding.

In 1973, Bliss and his colleagues Lomo and Gardner-Medwin showed that the pathway from entorhinal cortex to the dentate gyrus is accompanied by growth of post-synaptic effectiveness after tetanic stimulation of afferent fiber (Bliss & Lomo, 1973). At first it was discovered in the hippocampus, but now it is known that LTP phenomenon can be found in multiple parts of the brain including cerebral cortex, amygdala, cerebellum and many other parts in the brain of different species (Ledoux, 1990). It is considered that the activation of postsynaptic NMDA (N-methyl-D-aspartate) receptors by glutamate released during depolarization of postsynaptic membrane is the initial point of LTP (Bear and Malenka, 1994). Extracellular Mg^{2+} ions relief the voltage-dependent block and this follows by Ca^{2+} entry via voltage-dependent Ca^{2+} channels (VDCCs) to the postsynaptic dendrite membrane. Intracellular concentration of Ca^{2+} grows, which can be sufficient for starting LTP, but the whole process is not well understood.

Besides NMDA receptors, the generation of LTP involves activation of metabotropic glutamate receptors (mGluRs). It is assumed, that the specific agonist of mGluRs, trans-ACPD (3R-aminocyclopentane dicarboxylate), gives rise to the synaptic junction enhancement that, in turn, shows a reciprocal blockage with LTP depended on NMDA receptors (Bortolotto and Collingridge, 1993). The researchers also aim at determining a retrograde messenger, participating in the mechanism of LTP. Retrograde messenger is a chemical that is released from postsynaptic dendrite and diffuses back across the synapse to modify the release of neurotransmitter from the presynaptic terminal (Bear and Malenka, 1994). Studies suggest that the gas NO (nitric oxide) play role as a retrograde messenger in LTP (Williams *et al.*, 1993).

The term “long-term depression (LTD)” describes a lowering of transmission efficacy that is following low-frequency repetitive stimulations. It is the opposing process to LTP. The mechanism of LTD is not well understood in all brain regions, in

which it occurs. The most frequent neurotransmitter used during LTD is L-glutamate. It works on NMDA receptors, AMPA receptors, metabotropic glutamate receptors etc.

Organization of neuronal microcircuits involved in cognitive processing

The majority of excitatory neurons release glutamate as a neurotransmitter. The axons of those glutamatergic neurons are through synapses connected to other glutamatergic neurons. Those in turn are sending signal to different brain regions, depending on the axon's projection. Glutamatergic neurons give the excitatory signal to the GABAergic interneurons, and they, in turn, form the synaptic connection on the soma of glutamatergic neurons. Glutamatergic neurons may also have synaptic connections with cholinergic, serotonergic, norepinephrinergic neurons. Soma of these neurons are located in the basal forebrain, raphe nucleus (group of nuclei located in the brain stem), locus coeruleus (nucleus in the pons of brain stem) respectively. Nerve cells of all parts of brain are also known to interact with glia cells like microglia and astrocytes that release cytokines and trophic factors important in synaptic plasticity.

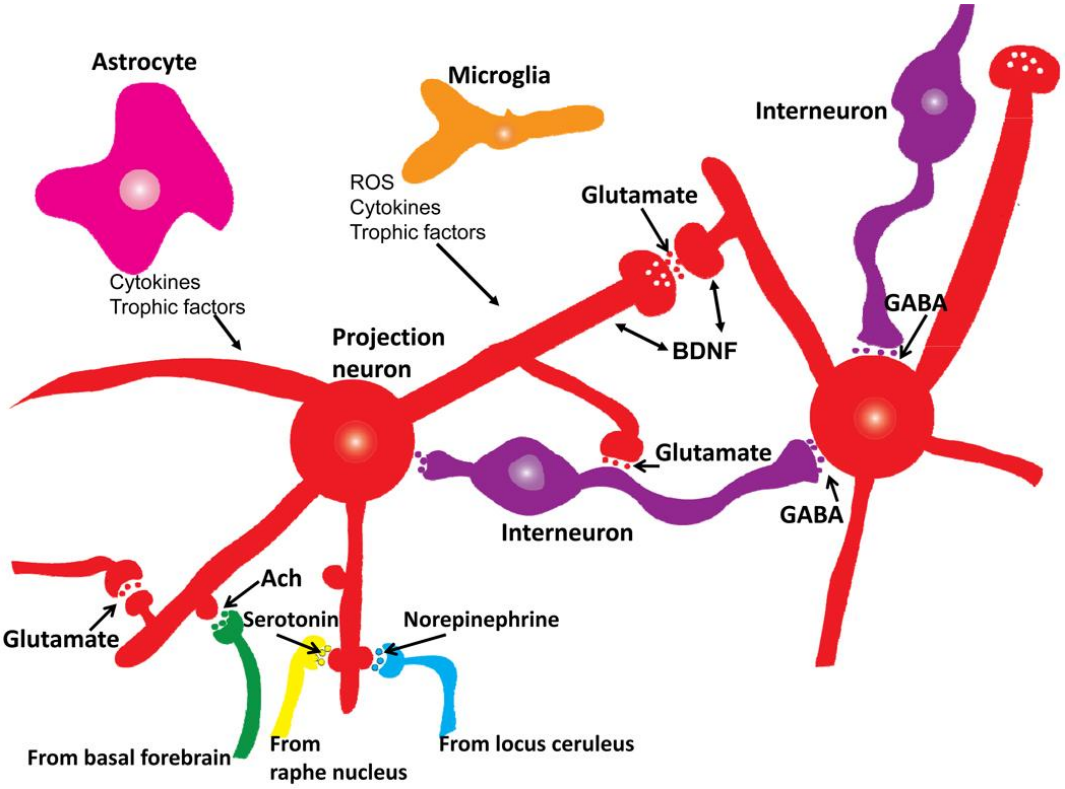

Fig. 2. Basic organization of neuronal microcircuits involved in cognitive processing. Ach: acetylcholine; ROS: reactive oxygen species; GABA: gamma-Aminobutyric acid; BDNF: brain-derived neurotrophic factor.

Basis of neural synchrony

Neural synchrony is represented by synchronized oscillations of membrane potentials of synaptically connected groups of neurons.

Neural oscillations

Neural oscillations, or brainwaves, brain rhythms, were first discovered in the beginning of 20th century by German psychiatrist Hans Berger. Oscillatory rhythmic activity is electrical neural activity in the CNS that is generated by neuronal ensembles and contains frequency bands from 0 to 300 Hz (Palop and Mucke, 2016). The precise role of oscillations is not yet determined, but possibly they mediate neural coding and neural binding.

There are three basic levels of organization of oscillatory activity: the micro-scale, meso-scale and macro-scale. Microscopic oscillations are the result of sequence of multiple action potentials (APs) generated by single neuron. These APs form spike trains – electrical pulses used for signaling and communication between neurons. They can be induced by physical sensory stimuli or abstract stimuli (such as memory encoding) and usually last as long as the stimuli are present. Spike trains can form regular rhythmic spikes or burst spikes (Wang, 2010). Mesoscopic oscillations are generated by oscillatory activity of group of neurons. Each neuron, as described above, generates APs, which result in rhythmic changes (spike trains), and through synapses the patters of these neurons can become synchronized. The synchronization is possible as a result of physical phenomenon such as interference (the APs are added up). Synchronized firing patterns allow synchronizing input in other cortical areas. The consequence of this is arise of large-scale oscillations and local filed potential. Macroscopic oscillations are the result of interaction between different brain areas. Here we should also take in consideration the time delays, as it takes time for signal to reach from one brain region to another. The important thing is if single neurons adjust the timing of action potentials in response to synaptic inputs from other neurons properly, because the synchronization of whole network depends directly on this (Wang, 2010).

Brainwaves are characterized by their frequency, amplitude and phase. They are mostly investigated using such techniques as electroencephalography (EEG), which is usually used to measure large-scale oscillations. EEG can distinguish different frequency bands: delta activity (1 – 4 Hz), theta activity (4 – 8 Hz, alpha activity (7.5 –

12.5 Hz), beta activity (13 – 30 Hz), low gamma (30 – 70 Hz) and high gamma activity (70 – 150 Hz). Group of neurons can increase or decrease the strikes frequency and synchrony and thus can generate higher or lower amplitudes of oscillations. *Alpha band* was the first described by Berger; alpha waves can be detected in the occipital lobe when the person is awake, relaxed and the eyes are closed (Klimesch, 1999), (William and Nathaniel, 1957). *Theta band* can be recorded both from inside the brain and from the scalp, for instance easily in the hippocampus. Theta can be detected especially during REM (rapid eye movement) sleep or active motor behavior. According to research of Klimesch et al. in 1994, semantic memory is related to alpha band activity whereas episodic or working memory correlates with theta band (Klimesch, Schimke and Schwaiger, 1994). In particular, alpha band tends to decrease in band power, and theta band tends towards increase (desynchronization/synchronization) relatively. *Delta oscillations* are associated with NREM (non-rapid eye movement) sleep and they are slow waves with high amplitude. *Beta oscillations* can be recorded during motor activity (as they can be detected mainly in motor cortex).

Gamma oscillations can be detected mostly in cerebral cortex and they are modulated by different mechanisms such as motor and memory tasks encoding, sensory processing, attention and other cognitive mechanisms (Uhlhaas *et al.*, 2009), (Sederberg *et al.*, 2007). These processes are accompanied by the increased gamma power, which are usually mapped directly in the task-related network (unlike the low frequency oscillations that involve different parts of cortex) (Crone *et al.*, 1998).

Network abnormalities related to memory loss in Alzheimer's disease

The questions why neuronal circuit and pathways are turning dysfunctional in response to high Aβ levels and how to prevent or drive back the progression of the abnormalities remain unanswered. Nevertheless it is known that encoding of memories and learning of an organism is directly associated with either single neurons or neural networks (microcircuits or larger distributed circuits) (Palop and Mucke, 2016). In the current stage of investigation of the network alterations, it is very important to focus the further research on the relation between hypersynchrony and altered oscillatory rhythmic activity, aggregates of pathological proteins and circuit dysfunction.

Alterations in neural oscillations activity and synchrony related to AD

Hypersynchrony

Hypersynchrony can be simply defined as increased synchronization of neural activity. It is a pathological phenomenon caused by proteins such as APP, tau protein, aβ or APOE4 (Apolipoprotein E4), which are overexpressed during AD (Palop *et al.*, 2007; Hunter *et al.*, 2012). Various researches have shown that epileptic seizures, resulted from network hypersynchrony, are very high risk factors for patients with AD, with average incidence 15.1% (e. g. Romanelli et al. 1990). In addition, study reports that patients with early onset of Alzheimer's disease are more likely to experience seizures (Amatniek *et al.*, 2006). Patients with seizures also tend to lose cognitive abilities much faster (Vossel *et al.*, 2013). Network hypersynchrony may be very important early characteristic of familiar AD (FAD) (Palop and Lennart, 2015).

Altered neural oscillation activity

Memory coding is enabled by oscillatory activity of theta and gamma bands (Gruber, Müller and Keil, 2002). Because one of the major impairment in patients with AD is memory loss, it is crucially important to understand, how the gamma oscillations are damaged. However, it has not been directly studied yet. What is known, is that EEG recordings from patients with Alzheimer's disease reported a decrease of power in gamma band (Herrmann and Demiralp, 2005). Task-related networks had shown a decrease in gamma power; default mode network (DMN, large scale brain network active during wakeful and resting state of the brain) had shown reduced decrease in lower-frequency oscillations.

hAPP-J20 mice model of AD has shown abnormal changes in power of gamma oscillatory activity (Verret *et al.*, 2012). During rest period we can observe spontaneous epileptic seizures.

Thus, pharmacological improving of brain rhythmicity can be great therapeutical option for treatment of Alzheimer's disease.

Neuronal dysfunction in AD

Synaptic dysfunction in Alzheimr's disease

APP is transported to presynaptic membrane and its presynaptical concentration increases (Palop and Mucke, 2010). In Alzheimer's disease, the APP is cleaved at the C-terminal of amyloid β by γ-secretase and at the N-terminal by β secretase. The outcome of this process is self-aggregation of amyloid β. This leads to generation of reactive oxygen species (ROS, reactive chemical substances containing oxygen) and as a result the membrane is peroxidated. This damages ion-motive ATPases and initiates the depolarisation of membrane. Intracellular concentration of Ca^{2+} raises and stimulates the release of glutamate from presynaptic stores. Consequently, signal transfer is impaired in neurons and lesions of axons and dendrites occur. Furthermore, amyloid β causes mitochondrial dysfunction and energy depletion in neurons (Cai and Tammineni, 2016). Altogether it worsens neuron degeneration and synaptic dysfunction.

Additionally, endoplasmic reticulum (which has Ca^{2+} stores) impairment causes the accumulation of misfolded proteins and it supports the nerve cell death.

Principal cells

Granule cells

Granule cells are types of neurons that can be characterized by small soma in comparison to other types of neurons and can be found in granular layer of cerebellum, dentate gyrus of the hippocampus, superficial layer of the cerebral cortex etc.Importantly, granule cell type is the principal cell type in dentate gyrus, forming a dense granular cell layer. Other characteristics of granule cells may differ depending on the brain area. For instance, one brain area can have GABAergic granule cells with axons, while in another brain area they are axonless. Granule cells in the dentate gyrus are generated in the adult brain (adult neurogenesis).

Autopsy of 83 brains H.Braak and E.Braak showed many NFT in granule cells of the fascia dentata. Presence of pathological protein was reported even on the V^{th} stage of AD. Still, NFTs in granule cells of fascia dentata are mainly the distinguishing characteristic of stage VI (Braak and Braak, 1991). The granule cell dendrites of healthy brain are long (approximately 15 μm), covered with spines (Einstein, 1994). Granules cells obtained from molecular layer of the hippocampus of

post-mortem brains with AD had shorter dendrites (57% shorter than control cases), decreased number of spines (44% of difference with control brains). Dendrites were found to mostly end at the point where plaque began. However, in some cases the dendrites where able to pass behind or through the plaques.

Pyramidal cells

Pyramidal cells are a type of nerve cells that can be found in the cerebral cortex, amygdala, hippocampus etc, and they are multipolar. It is named “pyramidal” due to its characteristic shape of soma – conic shape. Other anatomic features of these cells are single axon and apical dendrite, many basal dendrites and dendritic spines (Megias and Freund, 2001). They can be excited by glutamate neurotransmitter and inhibited by GABA.

In mammals, pyramidal cells are getting more complex from posterior to anterior brain areas. It was suggested, that the complexity of pyramidal cells is also increasing with growth of cognitive abilities (Elston, 2018).

Heiko and Eva Braak reported different neuropathological changes of pyramidal cells on different stages. On the stage III, neurofibrillary tangles start to appear in pyramidal cells of the subiculum (Braak and Braak, 1991). At the stage V, the amount of NFTs in subiculum increased and the tangles could be also seen in pyramidal neurons of CA1 (Braak, 1997). At this stage we can also find neuropil threads in subicular pyramidal cells. Small amount of NT were also found in CA1, CA2 and CA3. At the last stage, all the changes were more profound. Accelerated pyramidal cell loss during AD was suggested to be caused by neurofibrillary degeneration.

Purkinje cells

In 1893 Czech physiologist Jan Evangelista Purkyně described GABAergic neurons located in cerebellum and they were named Purkinje cells. Fukutani et al. reported Purkinje cell loss and synaptic alterations in dendrites in AD (Fukutani *et al.*, 1996). Even though human cerebellum is thought to be less affected area of brain during AD (Wisniewski, Wen and Kim, 1989), studies report a decrease of Purkinje cell density in this region. Purkinje cell loss is likely a result of neuropathological changes such as aβ and tau protein (Mavroudis *et al.*, 2010).

Interneurons

Interneurons are a special type of nerve cells that form 20-30% percent of neocortex (Markram *et al.*, 2004) and enable the transfer of signal between afferent and efferent neurons. They create circuits either with local neurons or they build a large network by connecting different brain regions. Most interneurons of CNS (central nervous system) are inhibitory and use GABA or glycine as neurotransmitters. They effectively control the excitability of principal cells and as a result control whole network synchrony (Buhl, Halasy and Somogyi, 1994). It is very important to understand the role of interneurons in neurodegeneration, as these specific cells are forming the circuits impaired during AD.

Dysfunction of inhibitory neurons in general probably reflects the impact of neuropathological amyloid β (Palop and Mucke, 2011). Aβ impact results in alterations in oscillatory activity and neural circuits. The principal interneurons impaired in AD are parvalbumin-expressing interneurons (PV, fast-spiking) and somatostatin-positive (SSP) interneurons.

PV interneurons are essential for network synchronization as they somatically and perisomatically inhibit the pyramidal cells (Freund and Buzsáki, 1998). Gamma oscillatory activity described above, depends on PV cells and play role in formation of cognitive function, and therefore decrease in gamma band leads to network hypersynchrony (Korotkova *et al.*, 2010). PV cells are also connected by gap junctions and form interneuronal network which modulate synchronous activity of pyramidal cells (Hestrin and Galarreta, 2005). Verret et al. tested hAPP-J20 mice and showed that network dysfunction and altered oscillatory activity are caused by PV interneurons (Verret *et al.*, 2012). A link between gamma oscillations and PV cells was also found by Sohal et al.; increase in firing rate of PV cells increased only gamma oscillations, whereas increase of firing rate of pyramidal cells increased only low-frequencies bands (Sohal *et al.*, 2009). As a conclusion, gamma activity depends on the inhibitory activity of PV cells. It was also found that in hAPP-J20 mice depletion of the voltage-gated Na^+ channel results in PV cells impairment (Palop and Mucke, 2016).

Another study suggests that Met-enkephalin, which can be found in hAPP mice and human brain with AD, could block μ-opioid receptors on inhibitory neurons and therefore inhibitory neurons could lose their biological function

(Meilandt *et al.*, 2008). It was reported that APP can also lead to alterations of L-type calcium channels on the interneurons, consequently leading to changes the Ca^{2+} concentration and function and plasticity of these cells (Yang *et al.*, 2009).

Circuit activity and memory encoding in the hippocampus is also controlled SSP interneurons, in particular by O-LM (oriens-lacunosum moleculare) interneurons. O-LM cells from healthy brain are distinguished from other types of interneurons by presence of spine, but the spine gain is absent during AD progression (Freund and Buzsáki, 1998; Schmid *et al.*, 2016). Data shows the impairment of these interneurons by aβ as well (Schmid *et al.*, 2016). It was found that APOE4-KI mice lose around 30% of SSP cells and this directly induces memory and learning ability alteration (Andrews-Zwilling *et al.*, 2010).

Summary

Alzheimer's disease is very serious and complicated type of dementia. Great progress has been made over the past years, but the precise mechanism of neuropathological changes is yet to be determined. AD is driven by different genetic and enviromental risk factors that develope over decades. Due to this fact it is difficult to find the appropriate therapy to reduce the impact of neuropathological changes. One of hte effective treatment could possibly be the inhibition of aβ production, or as an alternative aβ binding monomers that will prefent the aggregation of neurotoxic oligomers. It should be also taken in consideration that specific treatments appear effective only in some phases of the disease.

Interneurons play crucially important role in neural synchrony. In particular, PV cells are suggested to directly contribute to AD-related functional impairments, such as synaptic dysfunction, altered oscillatory activity and network hypersynchrony. Decrease in gamma power causes alteration in task-related networks and therefore affect memory encoding, learning and other cognitive abilities. Analysing the information above I can say that stimulation of PV and SST cells can improve network activity and as a result improve cognitive function. Nevertheless, theories should be thoroughly experimentally tested in different AD models.

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