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Neuronal Impulse Theory and Alzheimer's Disease

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Abstract

The paper gives a link to a mechanical hypothesis of the functioning and functionality of the brain. Mechanic impulses and pressure waves occur at the neuronal cell bodies and the neuronal fibers and conduct information. The requirement for these physiological aspects is a certain hydrostatic pressure in the neurons and an elasticity of the neuronal membranes. The alteration of the neuronal fiber walls due to the hydrostatic pressure in the neurons may be comparable with changes at the walls of arteries due to the blood pressure. In the older ages fiber breaks may occur with an escape of cytoplasm into the extracellular compartment and otherwise agglomerisation of the resting cytoplasm in the involved neuronal cell bodies. These two pathophysiological mechanisms may be important factors for the development of plaques and tangles.

Keywords: Amyloid plaques; Tangles; Neuronal cell pressure; Fiber cracks; Plaque toxicity

Introduction

The Alzheimer's disease is one of the most prevalent diseases of men. The incidence is growing as the lifespan of the elderly increases. The pathogenesis of the disease is not very clear. There are overlaps of the dementia of the Alzheimer's type with the apparently normal reduction of the mental activity in higher age groups. The atrophy of the brain and the size of the CSF spaces is less in the "non-pathological" senility than in the Alzheimer's disease. The neurons of the physiologically aging brain incorporate ageing pigments (lipofuscin, neuromelanin), however neuritic (amyloid) plaques and tangles are seen to a lesser extent.

The mechanic model of the neuronal activity presented in this paper is hypothetical. This theory has been formulated as early as 100 years ago [1,2] and the idea has not been taken up until the last few years [3-7]. Mechanical impulses are the basis of excitement and neuronal conduction in the nervous system. Mechanical stress of cell bodies and fibers can cause breaks at the fiber walls and such breaks can cause the development of plaques in the extracellular compartment. Aggregation of the resting cytoplasm in the cells can lead to the development of the intracellular tangles.

Plaques, tangles and threads are specific morphologic structures in the brain of people with dementia. However, there is no evidence that such structures are the real reason for the insufficient function of the brain. It is therefore certainly right to say that the Alzheimer deposits are a synergistic or modulating factor for dementia. Only the loss of neuronal cells justifies with a reasonable degree of probability the assumption of the reduction of the brain performance capability.

Morphology and Pathogenesis of the Alzheimer's Disease

In cases of the Alzheimer's disease tangles in numerous neuronal cell bodies and also neuritic threads in the only few µm thick fibers of the neurons are seen. The tangles show the same staining and optical properties as starch. They are visible by staining with Congo-red and exhibit birefringence to polarized light. The tangles share immunological properties with non-pathological membrane proteins and neuronal proteins (amyloid precursor protein, microtubules and neurofilaments). The plaques (about 50-200 µm in size), formed in the extracellular region, show a dense amyloid core and a larger granular structured rim [8]. Using electron microscopy at the rim of the plaques are seen many enlarged neurites containing shrunk mitochondria and dense bodies (which probably originate from degenerating mitochondria) [9,10]. The origin of plaques, seeing mainly in the cerebral cortex, is not clear. Generally is assumed that the amyloid proteins are produced by the neurons. The migration of the amyloid and preamyloid particles from the intracellular compartment into the extracellular space through the lipid membrane could be as a form of diffusion. However, the formation of the spherical plaques in this way would be highly unlikely. It would be probably that the preamyloid and amyloid particles tend to show a more diffuse deposition like the deposits at the walls of blood vessels in cases of amyloid angiopathy.

The tangles in the neuronal cell bodies consist mainly of amyloid beta peptides (Aβ) and paired helical filaments. The formation of the tangles arises from precursor proteins. Amyloid precursor protein is an integral membrane protein of the neuronal cell bodies and fibers. Amyloid beta monomers are soluble but in a high concentration, they undergo a conformational change to form a beta sheet-rich tertiary structure and form amyloid fibrils [11].

Tau protein interacts with tubulin to stabilize microtubules in the neuronal cell bodies and neuronal fibers [12,13]. Microtubules occur in large quantity in the neurites and form together with microfilaments and intermediate filaments the cytoskeleton of the cells and the fibers. In cases of Alzheimer's disease the tau protein condense as paired helical filaments inside nerve cell bodies as a major component of neurofibrillary tangles and inside dystrophic neurites of the neuropil. These deposits are stainable with Congo-red.

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Mechanical Impulse Theory in the Nervous System

Impulse waves and a certain hydrodynamic pressure in the neuronal cell bodies and neuronal fibers are the basis for the neuronal conduction of information. Neurons and its extents are liquid filled vessels (similar to hoses under pressure). Information or excitations accompanied by action potentials are conducted by pressure waves [3-6]. The basis for this mechanism is the mentioned hydrostatic pressure within the neurons and the elastic property of the fiber walls.

Associated with these premises it can be assumed that lipid membranes can tear. A membrane crack can lead to an efflux of neuronal plasma into the extracellular compartment. This efflux of cytoplasm can form the basis for plaques. Each neuron probably possesses a defined amount of fluid cytoplasm components, which contribute to the generation of plaques. The relatively uniform size of plaques in different areas of the brain may support this assumption. Larger cells form larger plaques and smaller cells may form smaller plaques. It is likely that a loss of a relative large amount of cytoplasm will lead to a substantial decrease of the hydrostatic pressure (turgor) of the affected neurons. The cell metabolism results in cell collapse and the loss of fluid causes a densifying of the remaining cytoplasmin the affected neurons. This densifying process of the cytoplasm may be a significant factor in forming tangles and threads.

Morphology of the Plaques and Possible Adverse Effects on Neighboring Neurons

There are also greater plaques in the cerebral cortex with a more spatial extension. Such plaques can be formed by merging of neighboring plaques [14] or the convergence of plasma from different fibers during simultaneous cracks of walls. It is also conceivable the escaped cytoplasm intermingles with fluid (lymph) of the extracellular compartment. The penetration of the plasma into the neuropil (neuritic and glial fibers) is the rule [8]. This is supported in particular by the fact that at the rim of the plaques are seen many distended neuritic fibers [10]. The coating of the neuritic fibers of such neighboring neurons due to the amyloid beta fibrils of plaques can disturb the function of the included fibers. The disturbed function could affect the extensibility and the elasticity of the fibers, leading to cell atrophy.

This could explain the findings of Koffie et al. who show in a mouse model of Alzheimer's disease that there is loss of about 60% of excitatory synapses in the neighborhood of senile plaques at a halo-like distance of about 50 μm [15]. This may also explain the findings of Rudinskiy et al. who found that the activity-regulated cytoskeletal-associated protein transcription (Arc/Arg3.1) lacks in the vicinity of plaques, generally robustly up regulated in relevant cortical networks following sensory experience [16].

Terry and Wisnewski (1972) propose that the earliest lesion seen in developing plaques is a distended neuritic fiber [10]. They suggest that the enlargement occurs at the presynaptic axonal terminals. This assumption supports the idea of possible ruptures of neurites as an initial mechanism in the development of plaques. Tangles and amyloid threads also can occur in atrophic or degenerated neurons without the incidence of plaques. An immediate link between a plaque and a tangle from one and the same neuron is seldom seen [8]. However, the distance between both of amyloid deposits may be large due to long axons.

How much Time is needed for the Formation of Plaques

It has been generally assumed that plaque formation is time dependent and a slow process. According to the impulse theory of the neuronal functionality and the possibility of fiber tears, plaques are formed as an acute event. For this suggestion would support recent findings of Meyer-Luehmann et al. (2008) using a novel in vivo multiphoton imaging technique. They could show that in a mouse model plaques are formed "extraordinarily quickly, over 24 h" [17]. Furthermore, "the plaques do not change in size after about the first 24 h, regardless of whether they had small or large diameters when they were first imaged" [17]. As a causal factor for this unexpectedly findings are discussed axonal trafficking defects [18].

Cerebral Amyloid Angiopathy

The efflux of a greater amount of neuronal cytoplasm into the extracellular compartment can explain the pathogenesis of the amyloid vasculopathy in cases of Alzheimer's disease. Also a delayed efflux of amyloid proteins through the lipid membranes due to an increased permeability of the membranes may contribute to the development of this vascular disorder. The small blood vessels will reabsorb the fluid and the soluble plasmatic proteins. Larger particles, particular preamyloid or amyloid particles, may be precipitated in and at the walls of capillaries, venules and arterioles. The incidence of the cerebral amyloid angiopathy in Alzheimer's disease is about 80% [19]. Drainage ways of the interstitial fluid (lymph fluid) between brain tissue and the external and internal CSF spaces, and also to the cervical lymph trunks are described [20-23]. The penetration and precipitation of amyloid proteins at the blood vessel walls of the brain of Alzheimer patients (amyloid vasculopathy) leads not uncommonly to deadly bleedings [24].

Comparison of the Neural Impulse Theory with the Blood System

A degenerative aging process at the neural lipid membranes is difficult to prove. The comparison of the neural pressure system with the blood pressure system could demonstrate analogies between the two systems. The blood vessels are more accessible for macroscopic, microscopic and functional characteristics of the arteriosclerosis. There is an increasing loss of elasticity of the walls of arteries with the increasing age of men [25]. Microscopic examination reveals local breaks of the elastic fibers. The causes for such breaks are a high blood pressure and turbulence in the blood stream. Both of these factors lead to an increasing strain especially to the intima of the vessel wall. Breaks of the elastic fibers can lead to enlargement (aneurysm) and thrombosis of the arteries or to intra and extramural bleedings [26]. Whether these changes in the blood vessels have parallels to changes in the walls of the neurons is speculative. Capillary (petechial) hemorrhages are most likely analogy to the formation of plaques caused by ruptured neuronal fibers in the cerebral cortex.

Reabsorption of Amyloid Proteins

The reabsorption of plaques and of "free" tangles (of died neurons) is inadequate and delayed. Without a monitoring of the progress the detailed knowledge about the quantity of the reabsorption of amyloid substances is difficult to obtain. There is probably a minor quantity of reabsorption, but the progredient course of the disease will effectuate a steady increase of amyloid deposits in the Alzheimer brain. Cruz et al. (1997) interpret the plaque morphology in the context of a dynamical model of aggregation and disaggregation of the plaque proteins [27]. But the size of plaques appears to remain relatively constant over a wide range of disease durations. The lack of the plaque growth is a strong point for the assumption that one plaque may be developed by cracks of one neuron or one neuronal fiber in a relatively short time.

In conformity with Ohnishi and Takano (2004) [11] the authors argue that the Alzheimer deposits are originated from harmless monomers of beta amyloid by aggregation of these proteins. Without an infectious agent, the generation of primary pathological proteins as a result of the reorientation of the anabolism and metabolism is not conceivable. The nucleus and the cell body of the affected cells are atrophic and the diameter of the nucleolus in tangled neurons is smaller than in non-affected cells suggesting that the metabolic activity is diminished [28].

Age and Quantity of Alzheimer Deposits

The appearance of tangles and plaques is exceptional in the brain of young men. This simple fact points to the increase of degenerative changes in the course of life time. If Alzheimer deposits occur in the brain of middle aged people the term pre-senile dementia is used. At this age the plaques often show a more homogenous or plasmatic feature. A pre-ponderance within families of patients with Alzheimer's disease could give evidence for a genetic disorder in these cases. However, plaques and tangles occur at least in a small number in almost all brains of oldest people [8] and therefore a genetic cause of the disease may play only a minor role. In cases of trisomy 21 (Down syndrome) Alzheimer deposits occur in young and middle aged patients [8].

Local Differences in the Frequency of Alzheimer Deposits in the Brain

In different regions plaques and tangles occur in different frequencies. The temporal lobe and especially the hippocampus is a strongly affected region. In the neocortex amyloid deposits are usually seen less frequently. Causes for the special vulnerability of the temporal lobe are not known. It may be that the enhanced vulnerability of certain areas in the hippocampus occurs due to additional disturbances (epilepsy, states after resuscitation) are a possible hint for this phenomenon.

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