Medical Hypotheses 82 (2014) 563–566

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Pressure waves in neurons and their relationship to tangled neurons and plaques

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ARTICLE INFO

Article history:
Received 9 November 2013
Accepted 8 February 2014

ABSTRACT

The paper based on the hypothesis that mechanical impulses cause the transmission of excitement in the peripheral and central nervous system. Possible connections between changes in the tubular neuronal network and the morphological findings of Alzheimer's disease are presented.

Additionally, changes in the viscosity of the neuronal cytoplasm and changes in the walls of the neuronal fibers due to the intracellular hydrostatic pressure and pressure waves are considered possible causes of plaques, threads and tangles. The pressure causes reduced elasticity and mechanical breakdown in neuronal fiber walls. This is compared to features found in blood vessels.

It is presumed that damaged membranes lead to an escape of cytoplasm from the neurons into the extracellular space. This outflow may cause the spherical structured proteinaceous plaques. On the other hand it could be that the decrease of fluid and reduced intraneuronal pressure after a membrane crack may favor the agglomeration of cytoplasm proteins in the neurons forming threads and tangles. The consolidation of the neuronal cytoplasm and the irreparable decrement of the intracellular pressure cause a loss of function and finally a dieback of the affected neurons.

The reduction of blood perfusion due to an increased local tissue pressure in certain regions of the brain may promote the forming of Alzheimer deposits. An increase of preamyloid proteins and small soluble amyloid particles within the extracellular fluid can lead, along their natural drainage route, to an amyloid angiopathy.

Introduction

Mechanical impulses, in this case pressure waves, cause neuronal transmission of information [1–6]. The occurrence of mechanical impulses in the brain is consistent with the occurrence of action potentials, which are generally accepted as mechanism for the propagation of neuronal information. However, accordingly to the mechanical impulse hypothesis action potentials and electric oscillations are an epiphenomenon of intense or less intense mechanical impulses in the neuronal fibers.

Beyond doubt the ramified fibers of the neurons represent a tubular network that is interconnected through synapses. The walls of the tubules are elastic and contain ion channels. Energy is required to allow the neurons to maintain a certain intracellular pressure (turgor) and an electrostatic membrane potential. This pressure is higher than the pressure in the extracellular space and is achieved by shifting of electrolyte through the cell membrane [7]. In all probability during the time of sleep this intracellular pressure and also the electrostatic membrane potential will be rebuilt.

A large part at least of somatic perception is based on mechanical effects on receptor cells [8]. An example of this is the Vater–Pacinian corpuscle. The required energy for the initiation, propagation and amplifying of impulses is supplied by the ionic currents (sodium and water influx during the initial phase of the action potential). These short time shifts of volume are using internal energy from electrochemical potential differences between the extra- and intracellular space. The mechanical impulses are initiated or reinforced through the opening of the ion channels that start during the distension of the neuronal membranes during the running mechanical wave [6]. The ionic currents are originally described in the famous investigations of Hodgkin and Huxley (1952) at giant nerve fibers of the squid [9].

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http://dx.doi.org/10.1016/j.mehy.2014.02.012
0306-9877/

Physiological and morphological characteristics of the Alzheimer's disease

Impulse waves in the neuronal network are comparable with the pressure wave in the vascular blood system. Particularly, a great part of the arterial walls consists of elastic lamellae. The capillaries consist of a monocellular layer of endothelial cells and an elastic basal lamina. The pulse wave of blood (palpable at the wrist) is provoked by the cyclic activity of the heart muscle. The speed of the vascular pulse wave is about 10–20 times faster than the blood stream in the same arteries [10]. The comparison of the blood vessels with the tubular system of the neuronal fibers is problematic as the neuronal tubules are much smaller than the blood vessels. However, the physical laws apply to both the arteries and the small neuronal fibers.

Comparative changes at the arterial vessels

The changes at the arterial vessels are described as "arteriosclerosis" (meaning reduction of elasticity), microscopic disruption of elastic fibers with local dilation of the vessel wall, atheromatous plaques, narrowing attachment of thrombotic material at the vessel wall (parietalthombosis), occluded thrombosis, aneurysms and miliary aneurysms, intramural and extramural bleeding [11]. This pathologic change gives reason to look for similar changes in the neurons.

Dendrite and axons represent tube-like extensions of the neurons. The fibers contain neuronal cytoplasm (axoplasm) and they are shielded by elastic membranes formed by cell membranes produced by oligodendroglial cells or Schwann-cells. The more tightly bound, or rather, the less elastic the membrane, the faster the propagation velocity of the impulse wave. Fibers with rapid pulse velocity (up to 120 m/s) possess myelin sheaths. The myelin sheaths consist of numerous dense stacked cell membranes which considerable can stiffen the walls of the fibers. Myelin sheaths are largely missing in the cerebral cortex ("gray matter"). In the "white matter" the fibers lay bundled in broad cords and nearly all of the fibers possess myelin sheaths.

Alzheimer deposits

The prominent microscopic changes that are found in brains of patients with Alzheimer's disease (plaques, also vascular plaques, tangles and threads) are detectable in the gray matter and especially in the cerebral cortex [12].

The biochemical characteristics of the deposits are widely known. The deposits consist of non-infectious amyloid-like proteinaceous material. Amyloid depositions exhibit an unusual compacted polarization-optic birefringent proteinaceous texture (beta-sheet structure) which is widely persistent in the metabolism.

Tangles

The appearance of amyloid structures in the neurons probably occur due to a disturbance of the cell metabolism. Microscopically the cells are shrunk and a good proportion of the watery cytoplasm is replaced by coagulated proteinaceous structures (tangles). The same structures are seen in the fibers, called threads. The degenerative process leads not uncommonly to the death of the cells, seen as "free" tangles. The authors assume that the cerebral amyloid is formed by the restructuring or the aggregation of the tertiary structure of the native proteins, meaning that the amyloid is not a generation of primary pathological proteins.

Plaques

Another distinctive feature of the Alzheimer's disease is amyloid plaque in the extracellular compartment. Plaques range from 5 to 200 μm across and are spherical amyloid proteinaceous precipitate. Most plaques consist of a dense core and a larger, granular rim with less density. Plaques of younger patients ("presenile dementia") often show to a lesser extent granular structures but a more homogeneous or aqueous feature.

Numerous mitochondria and dense bodies are seen by electron microscope in the rim of mature plaques, the latter probably originate from degenerating mitochondria [12]. The abnormal numeric concentration of atrophic and shrunk mitochondria argues for an origination from condensed neuronal cytoplasm.

The assumption that there is an increased pressure (turgor) in the neurons, in whose fibers pressure waves are running, let us also assume that cracks or mechanical breakdowns may occur at the tubular walls. In this way neuronal cytoplasm may escape into the extracellular space and may develop plaques.

Amyloid vasculopathy

The relative frequent coincidence of plaques and tangles with the amyloid vasculopathy of the brain is well known. There is a general belief that the brain failed to develop a typical lymph drainage. It is astonishing that in this connection the origin of the cerebrospinal fluid is not argued (see [13]). The smaller blood vessels reabsorb a large part of the extracellular fluid which comes into existence as a result of the blood circulation by outflow of blood plasma and probable to a minor extent from the outflow of cytoplasm from the neurons (independent of the outflow of cytoplasm from cracks in the walls). Therefore the extracellular fluid probably contains precursor proteins of amyloid or small amyloid particles.

It is conceivable that the extracellular preamyloid or amyloid proteins on their drainage way will deposited at the walls of capillaries, venules and arterioles and so may generate the amyloid vasculopathy. An increased pressure (turgor) in the neurons will promote the outflow of cytoplasm at the membranes. In a recent paper of a Japanese team of researchers is shown that amyloid beta is secreted through the cell membrane due to autophagosome into the extracellular space using a transgenic mouse model [14].

Reabsorption of amyloid

Plaques or tangles will only seldom be found inside and at the edge of cerebral infarctions or cysts of old infarctions in cases of Alzheimer's disease (unpublished observation, HB). Therefore it can be deduced that a minor lytic and absorptive activity or a microglial clearance [15,16] of amyloid proteins is probable in brain tissue necrosis. This phenomenon can be also meaningful for the pathogenesis of the cerebral amyloid angiopathy. However, plaques and "free" tangles probably are not significantly reabsorbed within an intact tissue structure.

The emplacement of amyloid beta into the walls of the small blood vessels may cause a weakening of the walls due to the reduction of elasticity. This can promote the development of miliary aneurysms and may be cause of dangerous and not uncommonly deadly bleedings in the old age [17].

It is ambiguous whether cracks of the walls of the neuronal fibers are the prime mover in the pathogenesis of plaques and tangles. The primary appearance of tangles and threads in the neurons as the initiation of the disease is also plausible. Amyloidosis due to multiple myeloma argues for an imbalance of assembly and degradation of the produced proteins. The causation for the occurrence of amyloid beta is probably an age-related degeneration or a