General mechanisms of nerve cell death

General mechanisms of nerve cell death in neurodegenerative diseases.

Etiopathogenesis and clinical manifestations of neurodegenerative diseases

In neurodegenerative diseases, some populations of nerve cells gradually disappear, which is associated with very serious psychological and neurological symptoms. **Mental** manifestations are manifested by loss of memory and mental abilities, behavioral disorders, often hallucinations, delusions and the overall decline of the personality; **Neurological** concerns are mainly concerned with proper coordination and control of movement and speech. These are serious diseases that place a heavy burden on patients, their families and society.

Neurodegenerative diseases

A common neurodegenerative disease is **Alzheimer's disease**, that affects 5 to 10% of people over the age of 65. In the initial stages, it manifests itself in memory impairment, but gradually leads to complete confusion and loss of most mental abilities.

Parkinsons disease draws attention to itself with tremor, muscle stiffness and limited mobility, but it can also have a number of psychological symptoms. The group of neurodegenerative diseases also includes **Huntington's disease**, **Creutzfeldt-Jakob disease**, various **ataxias** and many others.

Heredity of neurodegenerative diseases

Most neurodegenerative diseases are hereditary, ale heredity does not play an equally important role in all. E.g. it is very important in Huntington's disease, while it is little used in Parkinson's disease. Mutation either affects one gene or changes a longer stretch of DNA, affecting neighboring genes. In addition, in a single disease, there may be mutations in several genes on different chromosomes. This is typical of Alzheimer's dementia (mutations on chromosomes 21, 19, 14 and 1 are described). The development of neurodegenerative diseases begins with a genetic abnormality, such as a mutation that causes a biochemical disorder, where the synthesized protein may be missing, altered, or a new pathological protein may be produced. These changes have consequences in the altered metabolism of certain populations of neurons - for example, abnormal protein is deposited. This causes neuronal dysfunction, eg by decreased neurotransmitter release, which leads to clinical symptoms.

Neuronal death progression

Neuronal loss in neurodegenerative diseases tends to be relatively slow. However, each neurodegenerative disease has its own characteristic clinical course. For example, Alzheimer's disease, Parkinson's disease and Huntington's disease begin slowly and develop over a period of ten to twenty years. On the other hand amyotrophic lateral sclerosis progresses rapidly within two or three years. In any case, the rate of neuronal death in neurodegenerative diseases is much higher, than for example in apoptotic losses during the physiological development of the CNS. This suggests that apoptosis is not the only mechanism for neuronal death in these diseases.

Molecular mechanisms of neuronal death

The events that lead to neuronal death can follow the initial impulse at different speeds: from gradual to rapid. Each neuron has its own optimal intraneuronal biochemical conditions such as pH, water volume, glucose concentration, calcium ion, or ATP concentrations. These conditions deviate from the norm in neurodegenerative diseases. The deviation may not manifest itself immediately, it can cause the death of the neuron, for example, after several years of action.

The ways in which neurons die are different. One widely accepted theory is based on knowledge about aging. As neurons age, they naturally decrease. This suggests that neurodegenerative diseases are caused by accelerated aging. The decrease in neurons in the CNS is not evenly distributed. In life we lose the most neurons from the substantia nigra, followed by cortical neurons and the least affected by spinal motoneurons.

In the elderly, we commonly find high concentrations of 4-hydroxynonenaldolichol and 8-hydroxy-2-deoxyguanosine. Nonenal contributes to the damage to the structure and function of the cell membrane by increasing its sensitivity to the toxic effects of free radicals. 8-hydroxy-2-deoxyguanosine is an indicator of oxidative damage. It oxidizes proteins and structurally alters them. Indeed, altered forms of protein are found to an increased extent in the brains of older people.

Oxidative processes

Although the aging process damages neurons, it is not enough on its own for their rapid extinction. However, oxidative damage to neurons can lead to rapid neuronal death. **Oxidative stress** is caused by the increased production of reactive oxygen species and nitrogen, such as superoxide, hydrogen peroxide nebo nitric oxide. It

can also be caused by a failure of protective mechanisms involving superoxide dismutase(SOD) or glutathione peroxidase. Free radicals peroxidize the lipids of the plasma membrane, thus increasing its permeability to various molecules (calcium ions, water), which leads to deterioration of neuronal functions.

The cell has two mechanisms of protection against reactive oxygen species:

1. enzymes, which convert free radicals into harmless substances (eg. glutathione peroxidase, superoxide dismutase);
2. non-enzymatic antioxidants (eg. ascorbic acid, tocopherol).

If the balance between free radical formation and antioxidant protection is disturbed, the cell may die. There is evidence that free radicals play a role in neuronal death not only in ischemic lesions but also in Alzheimer's disease, Parkinson's disease or Huntington's disease. E.g. in Parkinson's disease, reactive oxygen species are formed in iron ion reactions during dopamine metabolism.

Excitoxicity

Another, and very important, mechanism of neuronal death is **excitotoxicity**. Most excitatory synapses in the brain use glutamate as a neurotransmitter glutamate. Glycine a GABA then act as inhibitory neurotransmitters. Glutamate binds to receptors, which are named after synthetic agonists:

1. **NMDA**: the agonist is N-methyl-D-aspartate;
2. **AMPA**: α-amino-3-hydroxy-5-methyl-4-isoxazol-4-propionate;
3. **KA**: kainate.

The excitatory activity of glutamate plays a major role in learning, memory and brain development. The attachment of glutamate to the above receptors causes subsequent sodium depolarization by influx. It therefore leads directly or indirectly to an increase in the level of free intracellular calcium. Excitotoxicity was discovered in 1970, when the ability of high concentrations of glutamate or aspartate to kill neurons was traced. Neuronal death or collapse of normal ion gradients in neurons can cause massive release of glutamate, which binds to adjacent neurons and their receptors, respectively. Increased extracellular glutamate levels create prolonged depolarization of neurons, causing prolonged calcium ion influx. The neurons thus affected swell rapidly and most often die of necrosis. For example, in amyotrophic lateral sclerosis, the spinal cord lacks a major transporter with high affinity for glutamate (EAAT2) expressed specifically on astrocytes. This was the result of an aberrant cutting mRNA, which eventually causes an increased level of available glutamate. One of the possible mechanisms is reduced protein synthesis, as can be seen, for example, in Parkinson's disease, where the synthesis of thyroxine hydroxylase in the remaining nigral neurons is reduced.. Template:Netisknout

Kategorie:Patobiochemie

Links

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