Exocitotoxicity of pathogenesis in the cns

Excitotoxicity in the pathogenesis of CNS disorders

Excitotoxicity due to excessive glutamate stimulation at NMDA receptors

Glutamate and its excitotoxicity

Glutamate plays an important role in the development of nervous tissue, its plasticity and during the transmission of excitatory signals at synapses . It is essential for the function of nerve tissue, but in large quantities it acts excitotoxically as a nerve poison.

The excitotoxic effects of glutamate are sometimes mentioned in connection with autism. However, its importance in the etiopathogenesis of this disorder is debated.

Effect of hypoxia on the brain

See the Hypoxia page for more information .

There are several reasons for the increase in glutamate levels. Hypoxia serves as a model example, as it is followed by events that result in excitotoxic damage to nerve tissue.

The brain is literally " *second to second* " dependent on the level of oxygen and glucose in the incoming blood. This dependence is due to the high metabolic activity of the nervous tissue, small energy intracellular stores and unconditional dependence on aerobic glucose metabolism. Decreased brain perfusion causes a critical shortage of energy resources. Neurons need more glucose and oxygen than they get. At the same time, they are flooded with glutamate. Lack of energy leads to incipient voltage failure, which, if lasted long enough, can result in failure of vital cell functions and, as a result, cell death.

A decrease in energy sources leads to a decrease in ATP levels , which limits the functions of ion pumps, such as the Na + / K + pump , which is necessary to maintain high intracellular potassium concentrations (155 mmol / l) and low intracellular sodium concentrations (12 mmol / l). l). Failure of the pump function leads to a decrease in the electrical gradient on the membrane (depolarization) and opening of voltage-gated ion channels. A cascade of events is activated, which results in cell death . Depending on the type of involvement, or the proportion of specific cells, there may be either *damage to specific groups of neurons* that are more vulnerable, or*damage to all neurons present in the area* , to stroke.

Immediately after ischemic injury, normal brain activity disappears due to the activation of potassium channels and the subsequent spread of hyperpolarization . This is probably due to the opening of potassium channels, which is affected by the local concentration of ATP, H + and Ca 2+ . *Opening may also be associated with alteration of non-heme metalloproteins and regulation of specific potassium channels* . This presumably protective response fails to maintain "energy-rich phosphate" levels, and both ATP and creatine phosphate levels decline rapidly in the minutes following ischemic injury . Decrease in pO 2 during ischemialeads to increased lactate production and the cell undergoes a Pasteur shift from dependence on aerobic metabolism to dependence on anaerobic glycolysis.

The resulting lactic acidosis lowers the pH of ischemic tissue from normal 7.3 to values ranging from 6.8 to 6.2. This value depends on the initial state - the amount of glucose that can be converted to lactate.

Potassium leaching leads secondarily to increased extracellular potassium concentration and massive gradual depolarization, which is also referred to as spreading depression . Rapid inactivation of O 2 -sensitive potassium channels may be one of the mechanisms by which nervous tissue prevents the increasing efflux of potassium . Other gradients are also lost.

Change in intracellular ion concentrations:

- the level of Na + and Ca 2+ is increased ;
- the level of Mg 2+ is reduced .Increased stimulation of the NMDA receptor with glutamate leads to an increase in intracellular calcium levels, which are at the beginning of the cascade of events leading to cell death

The extracellular concentration of many transmitters is increased during ischemia-hypoxia. Depolarization-induced influx of Ca 2+ by voltage-gated Ca 2+ channels stimulates leaching of the cell's vesicular pool, including the excitatory amino acid glutamate . Increased glutamate intake is associated with 2 Na + intake (according to older sources 3 Na +) and exclusion of K + and HCO 3 - / OH - .

As the gradient on the membrane progresses, the increased glutamate uptake is stopped .

Interestingly, these channels (GLT-1, EAAT2, EAAT3) can be affected by free radicals by oxidation of the redox side of the transporter. Due to the disturbed gradient, the direction of the transporter function can change . The above-mentioned phenomena are the essence of the increased concentration of glutamate in the ischemic brain, which can reach up to a thousand times its normal value.

Glutamate accumulating in synapses leads to massive stimulation of its receptors, which is usually toxic. Glutamate activates 3 classes of receptors :

- NMDA;
- AMPA;
- Kainate type.

These receptors alter calcium ion permeability due to glutamate stimulation (see figure). Ions then trigger a variety of lethal reactions, including nitrosative stress .

Diseases and therapeutic prospects

ALS - clinical picture We consider excessive stimulation of glutamate receptors to be the first cellular response in a stroke. Increased stimulation of NMDA receptors is also found in Alzheimer's disease , where it leads to increased production of APP (amyloid precursor protein) and subsequent accumulation of beta-amyloid . This receptor thus represents an interesting therapeutic target. However, a way remains to selectively block cell death-associated NMDA receptors and omit other, physiologically essential . The NR2B subunit, which has recently received increased attention, offers some hope . Today, these subunits are thought to be combined with other types, thus limiting possible therapies . One possible cause of failure is also a short therapeutic window. Last but not least, we encounter excitotoxic damage in one of the ten known forms of amyotrophic lateral sclerosis , when the superoxide dismutase gene (SOD1, 21q22.11, hereditary dominant and recessive) is mutated. Loss of SOD1 function then leads to increased oxidative stress, mitochondrial dysfunction, RNA destabilization , disruption of synaptic transmission, and glutamate excitotoxicity.

Links

https://www.wikiskripta.eu/index.php?curid=54306

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