CRITICAL REVIEW

CELL DEGENERATION IN PARKINSON'S DISEASE

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ABSTRACT
Parkinson's disease is a progressive neuro-degenerative disorder. The symptoms of this disease appear as a result of the progressive neuronal death of dopaminergic neurons in substantia nigra. Oxidative stress and mitochondrial dysfunction are two general factors, contributing to the disease development. These processes create free radicals, leading to dopaminergic neurons' death. The mechanisms, by which oxidative stress, mitochondrial dysfunction and free radicals formation participate in the neurodegenerative process, are described in detail. These mechanisms give a satisfying explanation to the clinical problems, related to long-term Levodopa usage in the Parkinson's disease treatment.

Introduction

Parkinson's disease (PD) is a progressive degenerative disorder, characterized by muscular rigidity, trembling and bradykinesia. Despite its unknown etiology, the symptoms of the disease appear as a result of the progressive neuronal death of dopaminergic neurons in substantia nigra (14,16).
Some hypotheses try to explain the nature and causes of this type of cell degeneration. A lot of studies show that oxidative stress and mitochondrial dysfunction are two cardinal factors, leading to the development of this process.
Oxidative stress and mitochondrial dysfunction are related to the formation of unstable free radicals (UFR). It is found that these free radicals contribute to the dopaminergic neurons loss in patients with PD. The mechanisms, by which oxidative stress, mitochondrial dysfunction and free radicals formation participate in the neurodegenerative process, will be described below. These mechanisms give a satisfactory explanation of the clinical problems, related to the long-lasting Levodopa usage in the PD treatment.

Mechanisms of the dopaminergic neuroprotection

*Oxidative stress(OS):*This is a process, in which unstable and potentially damaging molecules are formed. They contain non separated electrons, which could be easily "inserted" to impair the normal development of the tissue biochemical processes.
Mitochondrial dysfunction (MD): Mitochondria, as cell energy producing centers, are responsible for the formation, storage and redistribution of the live cells energy (mostly in the form of ATP). Mitochondria are also part of the cell defence against the toxic effect of the excessive amount of Calcium ions (Ca ++).They usually "absorb " the abnormal amount of this element. The dysfunction of the mitochondria, probably caused by free radicals, may initiate a process, called apoptosis. Apoptosis is also a process, related

to the so called "programmed cell death"(PCD)(18). Although there is some difference between the apoptosis and PCD, the two terms may be used as synonyms. The mitochondrial dysfunction, on its side, may also lead to the formation of free radicals (2).

*Diminished antioxidant protection: T*he diminished concentration of glutation, a basic antioxidant, could lead to an increase in the amount of free radicals.

Cytotoxicity: The cell excitatory hyperactivity (firing) of neurons outside of substantia nigra, could lead to neuronal death. This excytotoxicity causes an increase in the intracellular Calcium (Ca++), another mechanism for cell damage.

Deficit of a trophic factor: The trophic factor is of great importance for the normal cell development. An possible deficit could lead to the impossibility of the organism to recreate the normal function of the damaged cells.

Abnormal glial activity: The abnormal activity of glial cell subpopulations, surrounding dopaminergic neurons (DN), could be also a cause for a neuronal degeneration.

Although the mechanisms, leading to a premature and accelerated loss of DN are not well clarified, recent experimental studies in animal models prove that dopamine agonists have a neuroprotective effect.

How do the neurons die in PD?

The bodies of the dopaminergic neurons are located in substantia nigra. They synthesize, store and release dopamine, responsible for the regulation of the motor functions. The worsening of the motor functions in patients with PD is related to the progressive degeneration of dopaminergic neurons(4).

The rate of DNs death changes in the different areas of substantia nigra, as well as through the development of the disease and the intensity of the process.

The neuronal degeneration is different in every patient, and depends mostly on the patient's age(in the time of the disease beginning).The observation that the rate of neuronal degeneration is higher in the first 10 years of the development of the disease, is of special interest.

The studies for tracing up the levels of degeneration are not yet entirely standardized methodically as well as quantitatively. The results of different studies vary in large limits.

Mechanisms, leading to cell death

Necrosis and apoptosis

Neurons, as other cells, could die by necrosis (pathological cell death), or by apoptosis (programmed cell death), as well as by a combination of both mechanisms.

The process of necrosis develops as a response of different excessive impacts and is characterized by a damage of the cell membrane integrity (inflammation) (9).It is fallowed by swelling and rupture of the cell (**Fig. 1**).

The apoptosis is a genetically determined process, in which mitochondria play a central role. Morphologically it is characterized by a condensation of the chromatine and biochemically-by a fragmentation of DNA, leading to cells shrinkage and quick death (**Fig. 2**).

In both processes-apoptosis and necrosis, the oxidative stress is of main importance. The moderate OS induces apoptosis and the excessive OS is one of the causes for the cell necrosis. Both mechanisms are responsible for the dopaminergic neuronal death in PD, as well as in other neurodegenerative disorders (Alzheimer's disease,

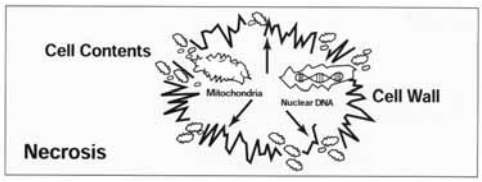

Fig. 1. Necrosis of the neuron.

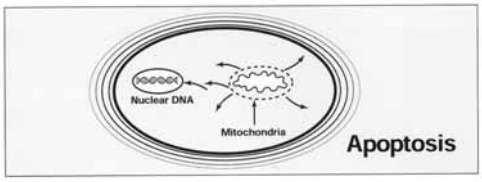

Fig. 2. Apoptosis of the neuron.

ALS).Some recent studies show the leading role of the apoptosis.

The concept for the oxidative stress, influencing the dopaminergic neurons in PD, is based on the fact that the metabolism of dopamine in substantia nigra leads to the release of free radicals. This way all factors and associated consequences are closely related and are at bottom of the dopaminergic cell death.

Oxidative stress

Free radicals show cytotoxicity because of their unstable condition and tendency for interaction. They could initiate different processes and eventually cause serious tissue damages.

In PD, the free radicals, as a result of the dopamine metabolism, may lead to a process of oxidative stress. An intermediate product, such as the hydroxyl radical, could start a sequence of pathological reactions leading to cells' death.

Since levodopa transforms to dopamine in substantia nigra, it may be considered as a indirect source of free radicals (19).In vitro studies with cultivated dopamine neurons show that levodopa undergoes a process of oxidative metabolism and the free radicals, as a result of this process, induce cell death by a mechanism of apoptosis. Clinical studies with levodopa do not indicate any toxic effect, due to the levodopa therapy(16,17,18).

The oxidative stress could damage irreversibly the cell by increasing the permeability of the mitochondrial transition pore (PTP-Permeability Transition Pore), a functional channel, responsible for the cell degeneration.

Mitochondrial dysfunction

As we already mentioned, mitochondria have a significant importance in the process of apoptosis. There are some data that the mitochondrial dysfunction leads to a decrease in the activity of the so called Complex 1 –a main component of the respiratory chain,this way reducing extremely the energy of the cell. This initiates the opening of the PTP and the release of factors, starting the process of apoptosis and cell death. The activity of the Complex 1 is lower in patients with PD, than in healthy persons (1,3).

Opening of the mitochondrial pore

Proapoptoic factors: Oxidative stress and increased intracellular Potassium are the mechanisms, causing the opening of the PTP. The opened pore releases some basic metabolic substances and the stored Calcium, thus activating a cascade of cell reactions, responsible for the apoptoic process. A Factor Inducing Apoptosis(FIA) and cytochrome-c are released. Experimental results prove that cytochrome-c turned out to be the universal signal for the beginning of apoptosis.

Protein with an antiapoptoic activity: Protein bc1 is probably an inhibitor in the mitochondrial pore opening and this way is a basic antiapoptoic factor. In vitro models

show that bc1 protein impedes the pore from opening and slows up the release of proapoptoic factors, such as cytochromec. Increased intracellular Calcium, oxidative stress, free radicals - all are factors, contributing to the opening of the mitochondrial pore.

Gluthation is an antioxidant, "cleaning" free radicals. It is known that the brain's gluthation is remarkably reduced in patients with PD. In these cases free radicals accumulation and neuronal degeneration increase are the most often observed processes.

Inflammation

The process of inflammation is accompanied by the increase of some inflammatory substances, such as interleukin-1 beta, interferon- gamma and TNF- alpha. Increased levels of these substances are found in patients with PD (8).

Abnormal glial activity

Glia, as a mediator between the blood vessels and neurons, is charged with important metabolic functions. There are some facts that a subpopulation of glial cells could contribute to the oxidative stress and release damaging inflammatory factors (7).

Excytotoxicity

The insufficiency of dopamine in substantia nigra leads to an hyperactivity of the excitatory glutamate-releasing neurons in nucleus subthalamicus. In normal conditions these neurons release glutamate, which reacts with the dopaminergic neurons, banding to some specific glutamat and N-methyl-D-aspartate receptors. This is an important physiological mechanism, controling the motor functions (15). In PD, the diminished dopaminergic neurotransmission leads to an excitatory hyperactivity of glutamat –producing cells and an excessive linkage to the NMDA receptors for glutamat. Excytotoxicity is the cause for the increased Calcium influx. The excessive invasion of Ca++ into the cell has a strong neurotoxic action and contributes to the opening of the mitochondrial pore. This activates some catabolic enzyme systems-phospholypases, proteases, kinases and others(12). The increased catabolic processes produce free radicals and nitric oxide with the formation of oxidative stress and apoptosis. These processes form a vicious circle and lead to the progression of the disease (**Fig. 3**).

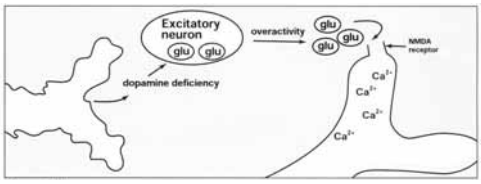

Fig. 3. Excytotoxicity.

Deficit of trophic factors

The trophic factors, known as factors of the growth, are important for the normal development and survival of the cells. These factors take part in the recovery of the damaged cells.

The processes of apoptosis are mutually related and form a vicious circle. The oxidative stress provokes a mitochondrial dysfunction, which on its side intensifies the oxidative stress. Both mechanisms generate free radicals. Exactly for the oxidative stress, the changed glial cells could lead to the PTP opening and thus initiate apoptosis and excytotoxicity. The latter one is probably caused by some pathologically changed cell processes and is increased by the mitochondrial dysfunction (**Fig. 4**).

Neuroprotection of the damaged dopaminergic neurons, slowing and stopping of

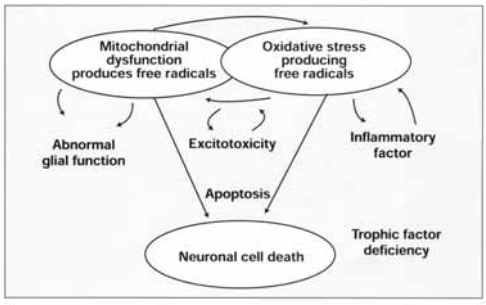

Fig. 4. Pathologic cascade of the throphic factors deficit

the neuronal degeneration are the ideal therapeutic clues in the treatment of PD, a progressive and disabling disease. This purpose could be achieved only by intervention in the basic pathogenic mechanisms, causing neurons' damage.

Drugs, which reduce the oxidative stress and discontinue the pathologic cascades, lead

to the slowing of the progressive loss of dopaminergic neurons. Treatment, providing neuroprotection, considerably influences the development of the disease and induces some neurons to re-establish their functions(5,6).

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