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PATHOPHYSIOLOGICAL BASES OF OXIDATIVE STRESS DEVELOPMENT BY EXAMPLE OF HUNTINGTON'S DISEASE

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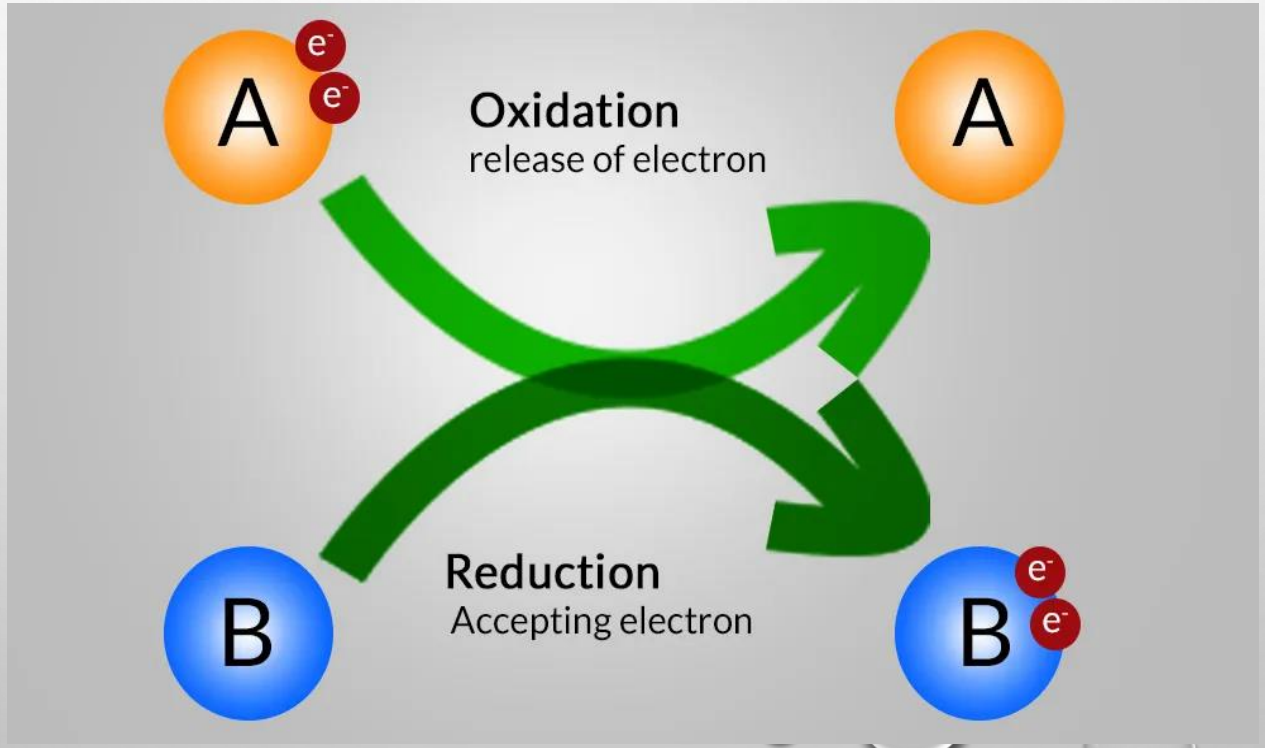
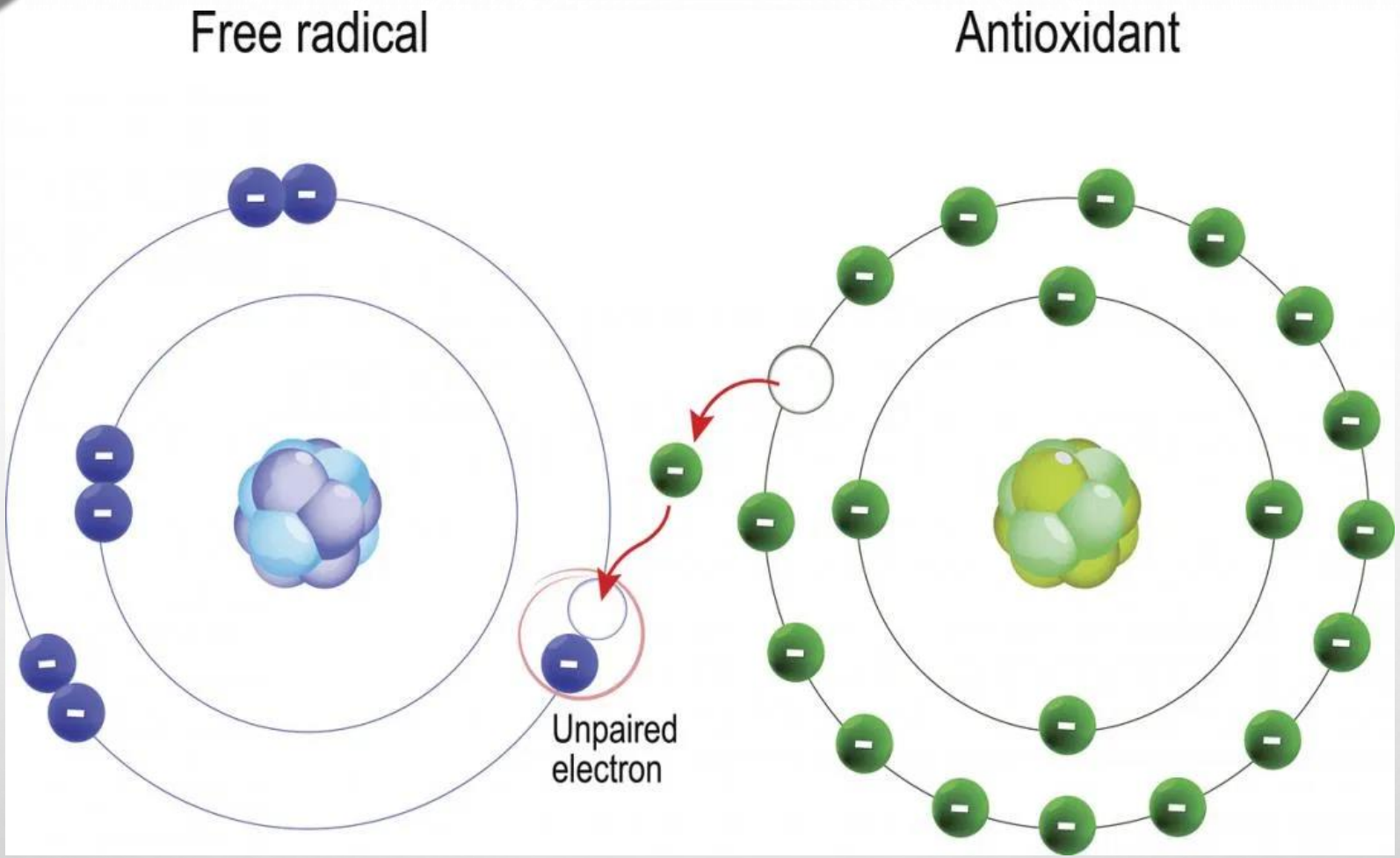
Oxidation is a physiological complex of aerobic reactions that provides energy supply of enzymatic-metabolic activation (with producing radicals) of all body functions. Radicals are constantly formed in a healthy organism and are necessary for the formation of immunity in the fight against bacteria and mutating cells.



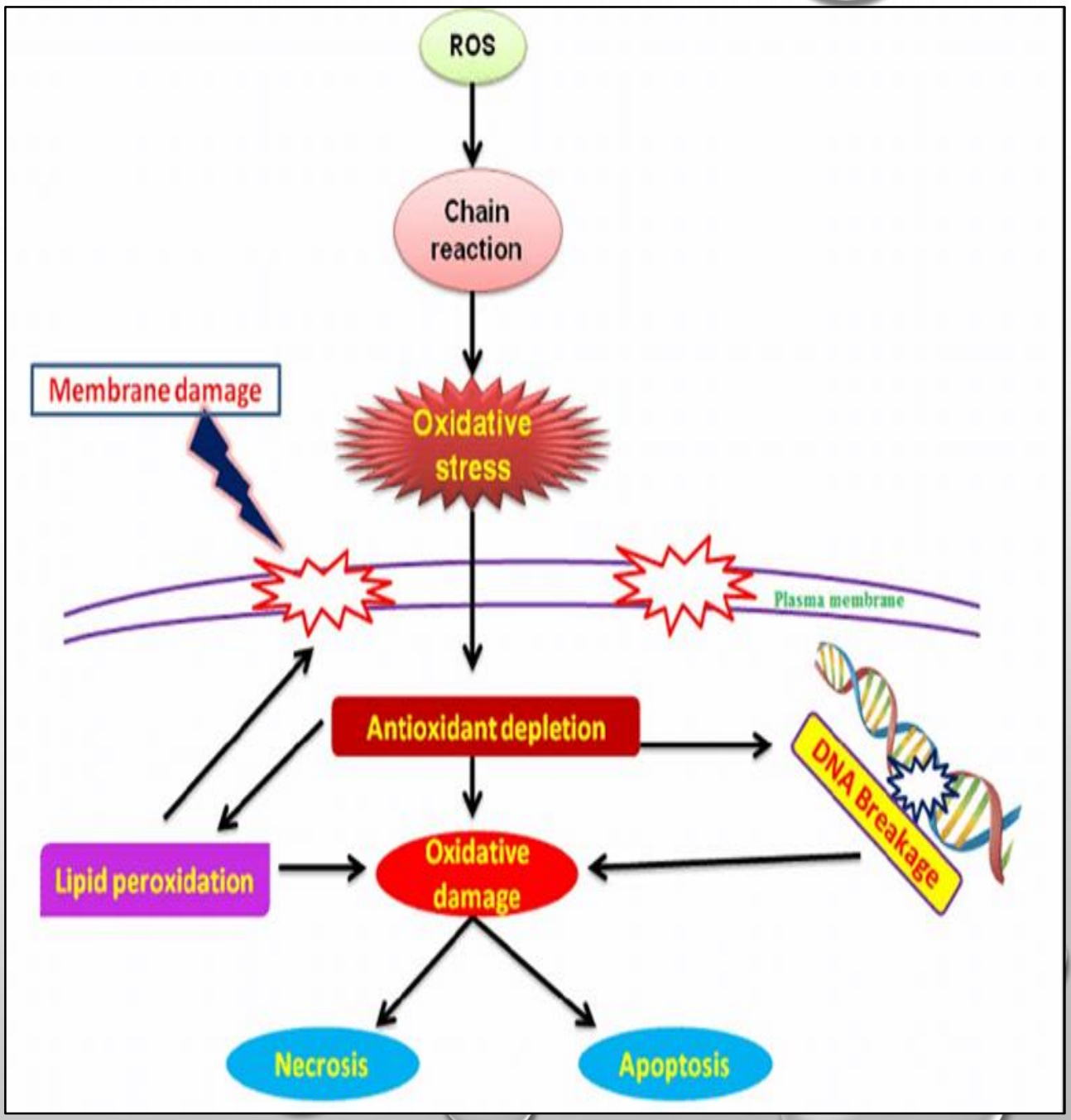


Radicals (active forms of oxygen, peroxides) are naturally formed: when fatty acids are oxidized as an energy substrate and normally neutralized by an antioxidant system; Lipid peroxidation, a necessary process in updating cell membrane phospholipids; Induced local oxidative stress (contact of immunocompetent cells with antigen for its destruction).

However, under the influence of harmful factors (ionizing radiation, taking drugs, tobacco smoke, stress or heavy physical activity), the amount of radicals increases dramatically, especially with lipid peroxidation and begins to have a damaging effect at the cell level, which manifests itself as oxidative stress.

Oxidative stress is a condition in which there are too many radicals in the body, triggering a chain reaction that violates the integrity of cells, leads to their damage or death.

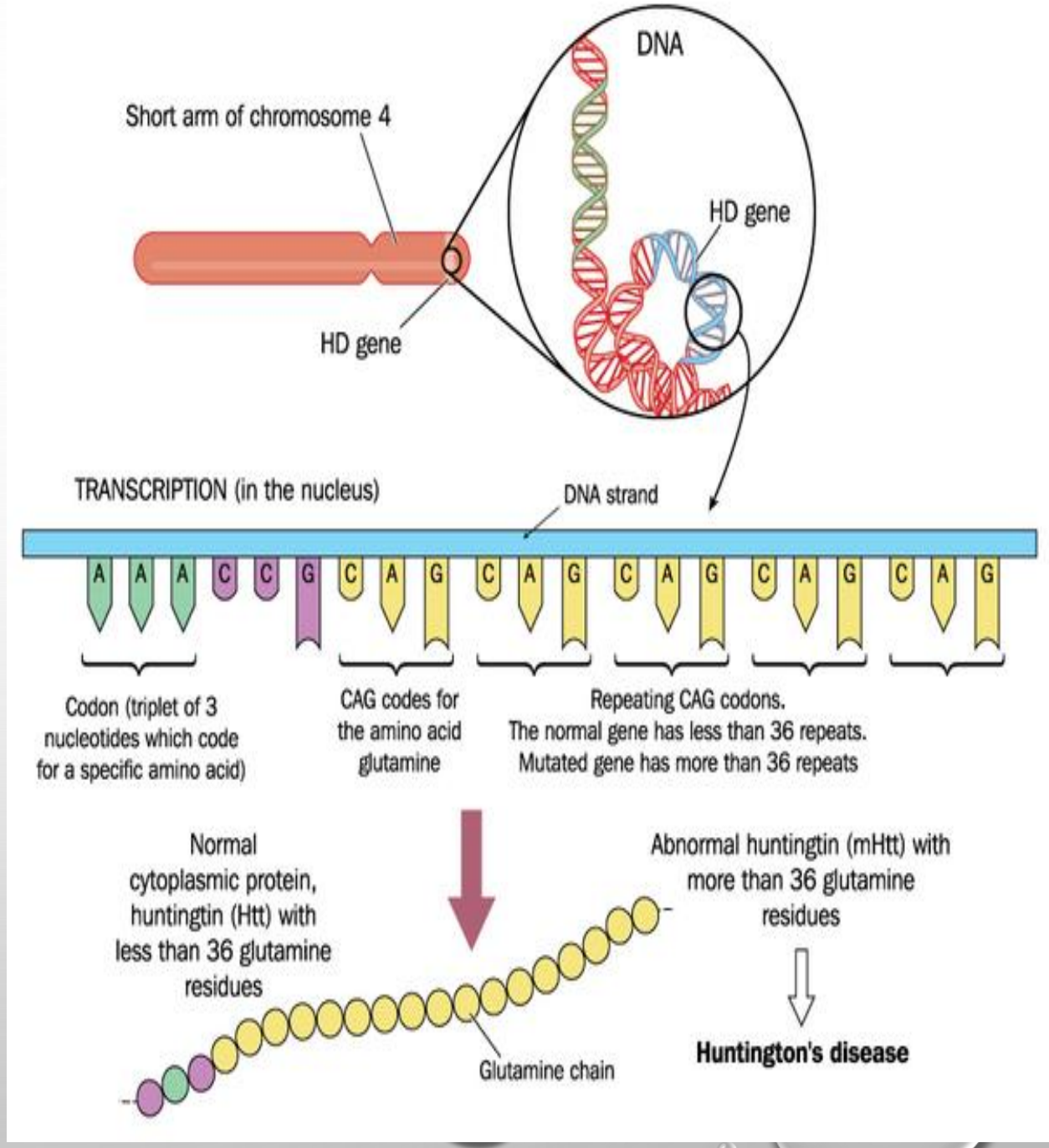
Oxidative stress provokes the development of many serious diseases, exemplified by the Huntington's chorea.



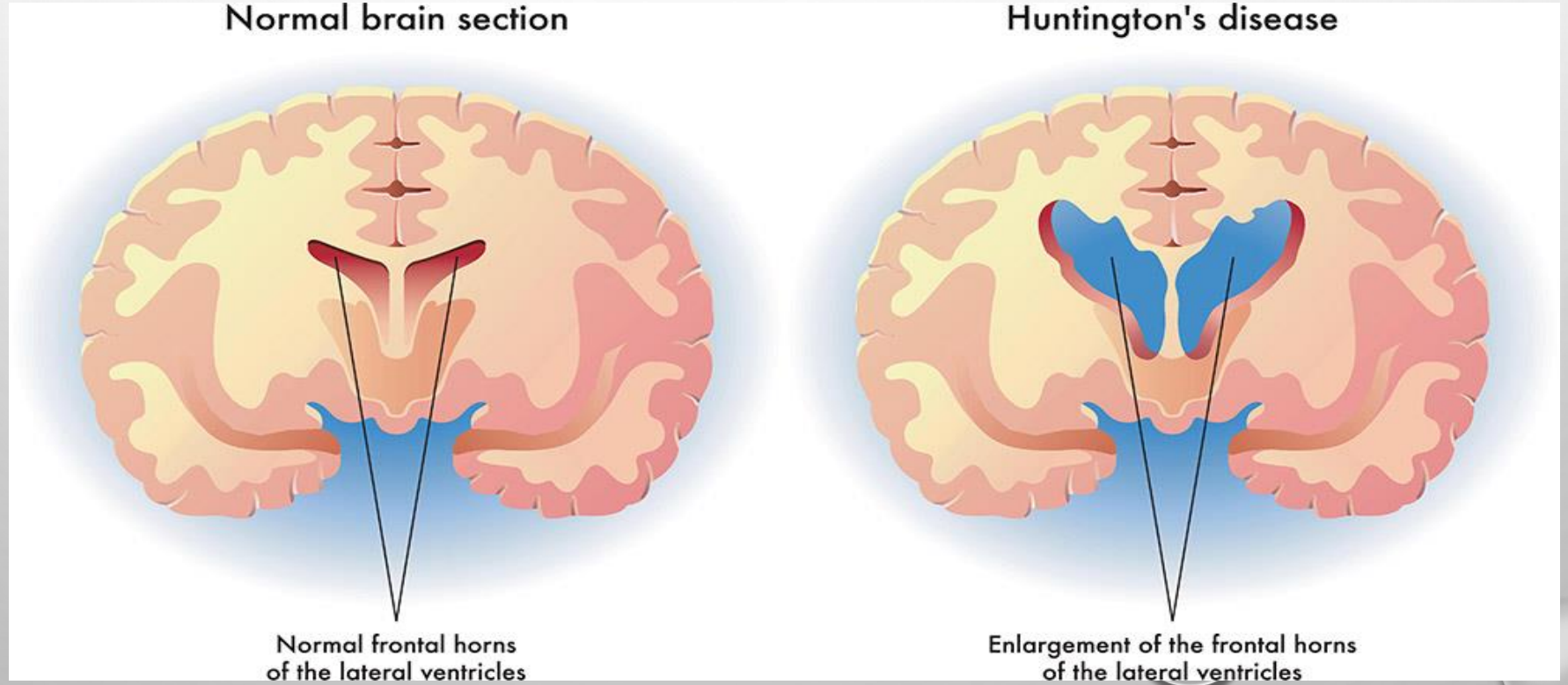
Huntington's chorea is a chronic progressive hereditary-degenerative disease characterized by choreic hyperkinesis and other extrapyramidal disorders, mental disorders and dementia.

The molecular basis of Huntington 's disease is the expansion of CAG repeats (CAG) in the IT-15 gene, which is located on the short arm of the 4th chromosome (4p16.3). Healthy people have 10 to 35 repeats of the DNA molecule in the fragment. In the mutant gene, the number of repeats increases significantly, from 36 to 120.

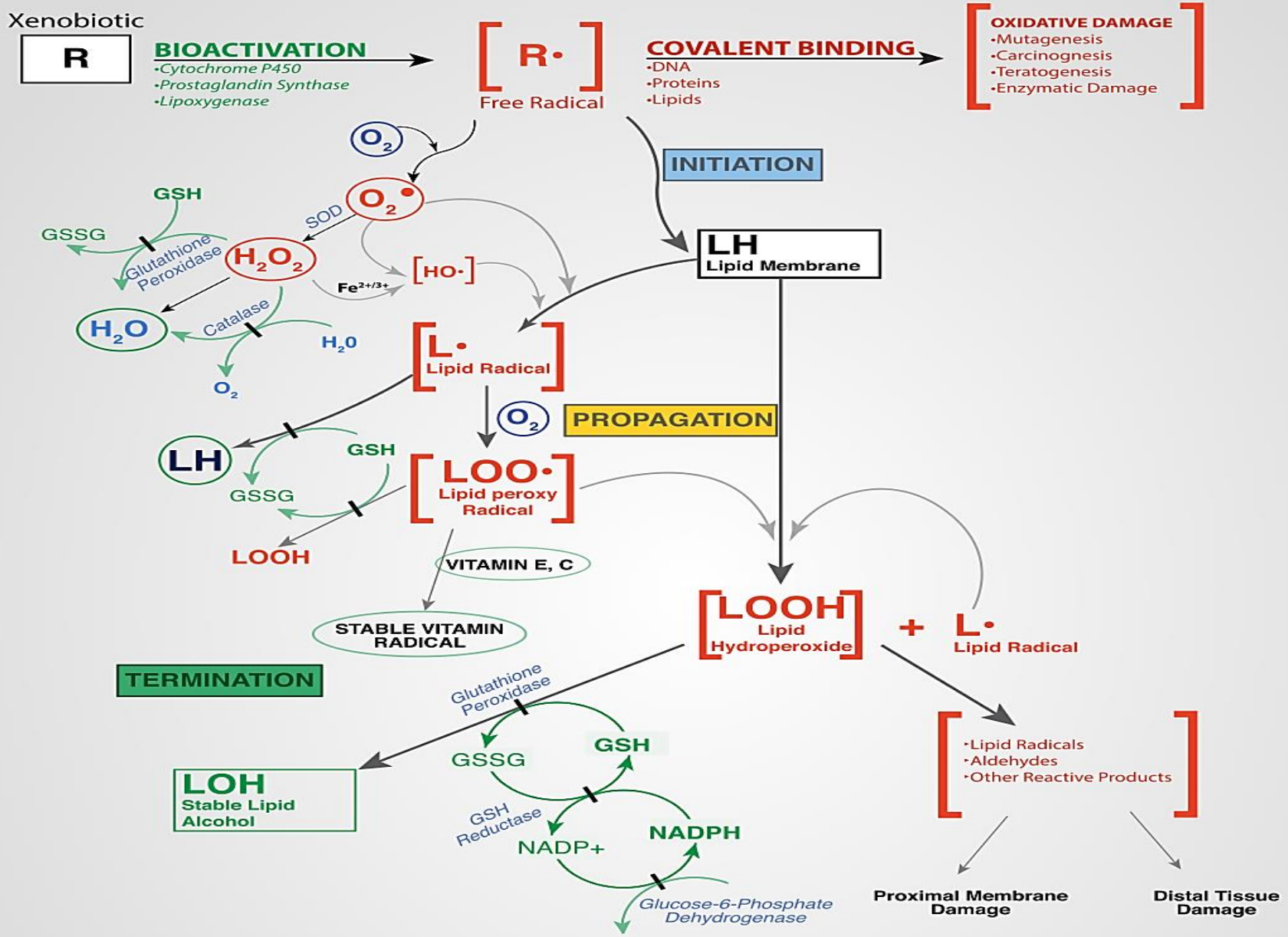
The gene is responsible for the synthesis of gentingtin protein, which is produced in the brain, most actively in the neurons of the cortex and cerebellum. The protein is present in both the cytoplasm and nerve cell nucleus. Cytoplasm`s gentingtin may be involved in the transport of vesicles and in the maintenance of the cytoskeleton. Based on experimental data, it has been found that gentingtin proteolysis produces fragments containing polyglutamines that are toxic to brain cells. Normally, their number is small and they are quickly disposed of involving a system of specific enzymes.

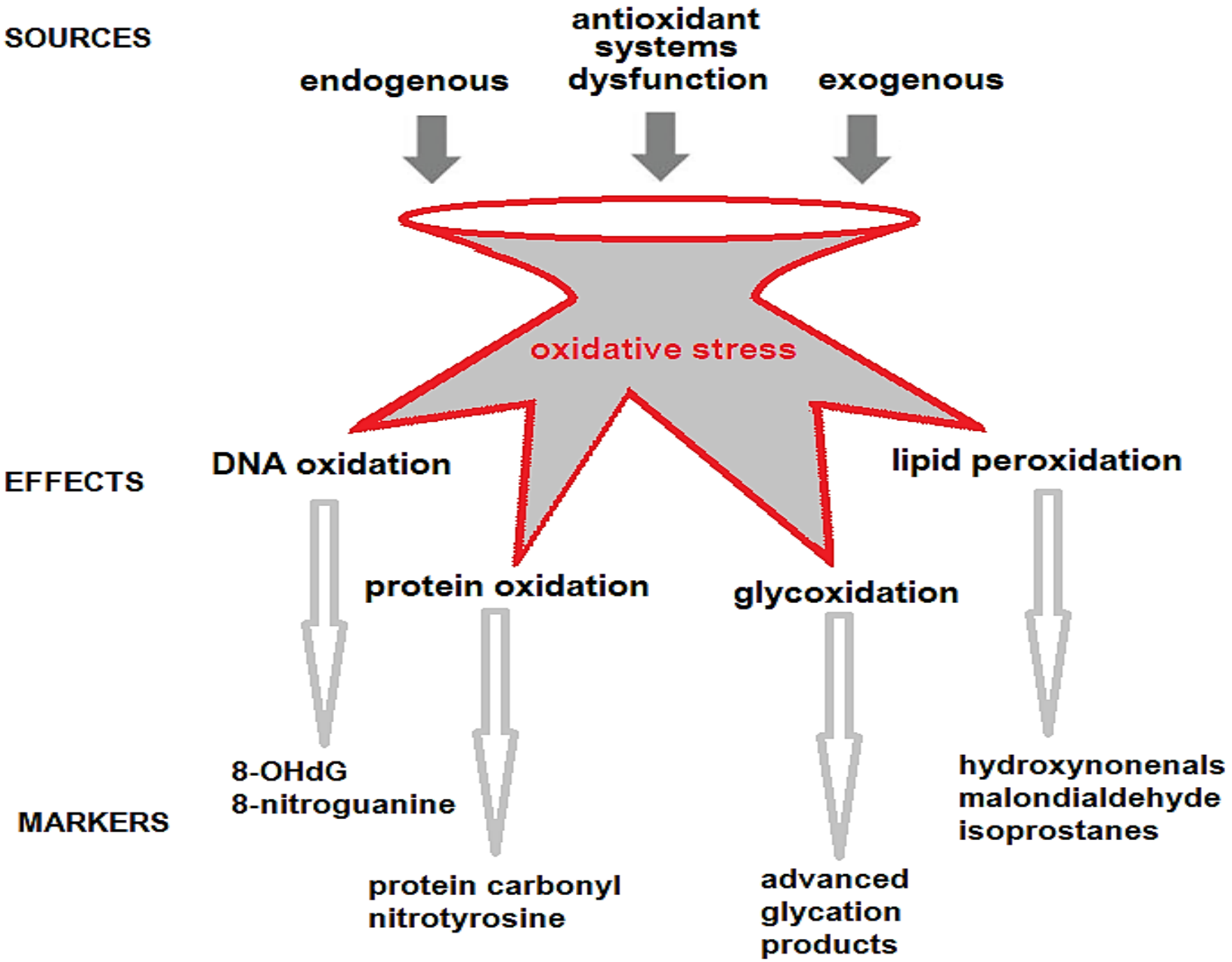


The denaturation rate of the defective protein is significantly higher than that of normal, leading to accumulation of gentingtin residues in neurons. Oxidative stress plays a significant role in the development and rapid progression of neurodegeneration with the accumulation of lipid peroxidation products. Excessive formation of lipid peroxidation products has a damaging effect at the cell level. Peroxide radicals interact with fatty acid molecules to form highly toxic hydroperoxides and a new radical. Such an avalanche process forms new and new oxidation chains involving primary (diene conjugates), intermediate (malonic dialdehyde, etc.) and final (Schiff base, etc.) products of lipid peroxidation, the continuous accumulation of which destabilizes membranes and promotes cell degradation. The most vulnerable are striped body cells receiving impulses from the crust of large hemispheres.

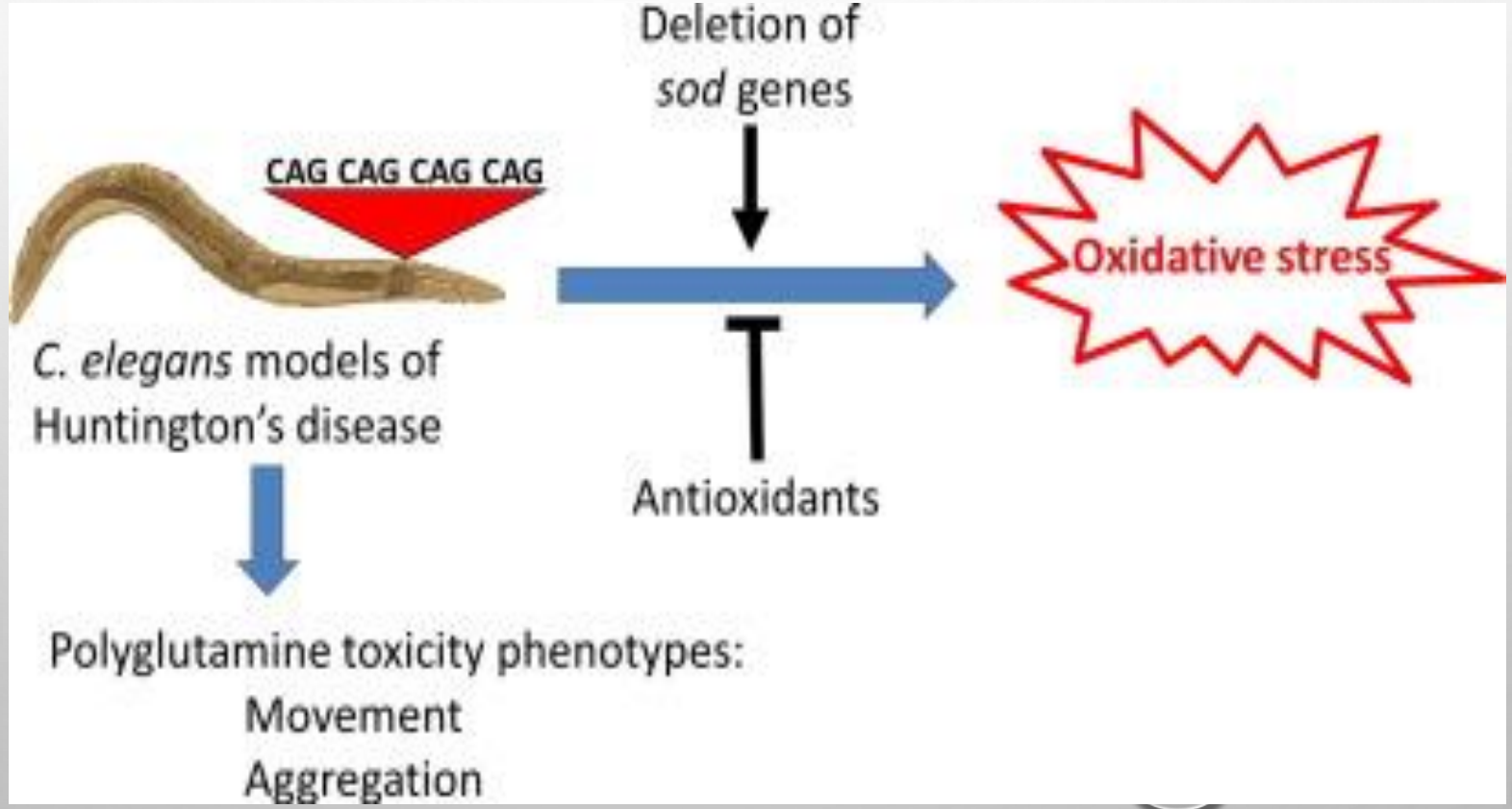


FREE RADICAL TOXICITY




SOURCES
antioxidant systems dysfunction
endogenous
exogenous
oxidative stress
EFFECTS
DNA oxidation
protein oxidation
glycoxidation
lipid peroxidation
MARKERS
8-OHdG
8-nitroguanine
protein carbonyl
nitrotyrosine
advanced glycation products
hydroxynonenals
malondialdehyde
isoprostanes

This results in inevitable cumulation (accumulation) of free radicals and the effect of accumulation of mutations during life. Despite of an effective system of antioxidant protection of the body, the level of formation of radicals in this disease exceeds the power of antioxidant potential. Thus, along with gene transcription dysfunction, there is a progressive build-up of oxidative stress. Oxidative stress should be seen as an inevitable process - one of the main reasons for Huntington 's chorea.

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