C26 ROLE OF MITOCHONDRIA DYSFUNCTION IN THE DEVELOPMENT OF INHERITED PREDISPOSITION TO THE DISEASES INVOLVING ENHANCED OXYGEN RADICAL FORMATION IN THE RATS WISTAR/S.

By selecting and inbreading Wistar rats which are sensitive (S) or resistant (R) to the cataleptogenic effect of gallocele the S and R inbred rat strains were created. Intense generation of oxygen radicals and enhanced lipid peroxidation were revealed in the liver and myocardium of the S rats. DNA rearrangements were found in the genome of S rats. Decreased oxidative phosphorylation and the lower respiratory control ratio were found in liver mitochondria of S rats. The formation of protein carbonyl groups and membrane fluidity were increased. SOD and catalase activity were decreased. Tumors, premature aging (low fecundity, growth retardation and short life-span), cataracts, cardiomyopathy-like changes in the myocardium, scoliosis are the characteristics of the S rats.

It was found that dysfunction of rat liver mitochondria is increased with age. Moreover, the increasing of mitochondria dysfunction is in good correlation with oxygen radical formation (low fecundity, growth retardation and short life-span), cataracts, increased with age. Moreover, the increasing of mitochondria dysfunction is in good correlation with oxygen radical formation (low fecundity, growth retardation and short life-span), cataracts, cardiomyopathy-like changes in the myocardium, scoliosis are characteristics of the S rats.

We suppose that mitochondria dysfunction plays an important role in the development of inherited predisposition to the enhancement of oxygen radical generation in the rats Wistar/S resulting in multipathological states.


C27 OXIDATIVE STRESS AND CELL DEATH DURING MOUSE DEVELOPMENT.
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One of the mechanisms thought to trigger programmed cell death is the accumulation of reactive oxygen species (ROS). Increase in ROS has been correlated with cell death caused by growth factor deprivation or by lissing signals such as the tumor necrosis factor. Accordingly, addition of antioxidants or overexpression of superoxide dismutase have proved to protect from cell death in different systems. Here we report that addition of antioxidants to murine developing limbs in culture prevents digit individualization and the typical cell death observed in the interdigital zones. In situ detection of ROS defines the interdigit as areas containing cells under oxidative stress. Cells under oxidative stress showed integral nucleosis and did not overlapped with those stained with acridine orange indicating that rise in ROS levels may be an early event during the course of apoptosis. Interestingly, many regions undergoing cell death in the midgestation mouse embryo correlate with those with a significant higher level of ROS. Our data suggest that generation of oxidative stress is a common requirement for the cell death occurring during mouse embryonic development.

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C28 GLUTAMATE CAUSES ENERGETIC METABOLISM ALTERATIONS AND FREE RADICAL FORMATION IN RAT CEREBELLAR GRANULE CELLS
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The excitatory neurotransmitter glutamate plays a major role in the pathogenesis of neuronal cell damage associated with various neurological diseases. Although mechanisms underlying glutamate induced neuronal damage are not yet fully understood, many intracellular processes are thought to contribute to the development of excitotoxic injury. In order to gain insight into the mechanism through which glutamate neurotoxicity occurs, cerebellar granule cells (CGCs) were exposed to glutamate and 1) glucose uptake, 2) oxygen radical production, and 3) mitochondrial respiration, were investigated.

1) Glutamate-exposure of CGCs stimulates glucose uptake in a temperature- and time-dependent fashion. This effect is inhibited by MK801, a selective antagonist of NMDA receptor subtypes, is more clearly in evidence when CGCs reach maturity in vitro and is also triggered by specific ligands such as NMDA, kainate and quisqualate.

2) Glutamate-exposure of CGCs is very rapidly accompanied by generation of oxygen radicals, O2* and O2, and by the appearance of mitochondrial oxidative activity, suggesting a major role for this enzyme in oxygen radical formation. Antioxidants, reducing agents and superoxide dismutase partially protect CGCs against glutamate toxicity.

3) Glutamate-exposure of CGCs causes impairment of glucose-dependent oxygen uptake and progressively affects mitochondrial respiration by succinate in the presence of ADP. As a result bioenergetic alterations a marked increase of cellular NADH concentration was found in glutamate-treated CGCs.