The Effect of Xenobiotics on the Respiratory Activity of Rat Heart Mitochondria and the Correlation with Superoxide Radical Formation

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Due to the wide use of chemicals and the permanent development of new compounds the environment is increasingly burdened by new chemicals in addition to the old ones. Many of these chemicals are stable and accumulate instead of being degraded. Biological organisms are particularly susceptible to lipophilic compounds since they readily accumulate in lipophilic compartments such as the central nervous system or biological membranes. This may become deleterious when those membranes are loaded with these lipid soluble substances which display central bioenergetic functions in the regulation of bioactivation of the entire organism. Mitochondria are a good example in this regard since these organelles are ubiquitously present in all tissues thereby representing a great volume for solubilization of lipophilic compounds. More important however is the fact that the many functions of these organelles, namely the generation of ATP via terminal cell respiration, is performed in the lipid membrane of mitochondria. Accumulation of foreign lipophilic compounds may therefore affect these bioenergetic functions by alterations of the hydrophilic/hydrophobic interaction of the enzymes involved. This assumption was recently supported by the observation that toluene accumulated in the membrane of isolated mitochondria affects energy conservation and the control of electron transfer via components of the respiratory chain.[1] Another consequence was the release of $O_2^{\cdot-}$ radicals as a byproduct of respiration. Although we were unable to explain the exact mechanism of these alterations we have some evidence that the biophysical property of the membrane determines the establishment of these toxicological activities. Thus, it was of interest to investigate lipophilic environmental pollutants which may be considered to exert similar effects on mitochondria due to their high partition coefficients. The effects of the xenobiotics **atrazine**, **benzene**, **butylated hydroxyanisole**, **butlyated hydroxytoluene**, **lindane**, **toluene**, and **xylenol** on the respiration of isolated rat heart mitochondria were studied. Bioenergetic parameters such as respiratory control (RC) and ATP/oxygen (P/O) values decreased considerably in the presence of these substances and a concomitant increase of superoxide radical formation was observed. These observations were discussed in terms of partial damage of the inner mitochondrial membrane, impairing the maintenance of the proton gradient across this membrane. In the presence of protons, ubisemiquinone radicals present in the inner mitochondrial membrane are able to react with molecular oxygen, thereby generating superoxide radicals. The changes of membrane potential, RC and P/O values show a good correlation with increased superoxide formation in most cases.

1. Nohl, H. and Stolze, K. (1992) Ubisemiquinones of the Mitochondrial Respiratory Chain Do not Interact with Molecular Oxygen. Free Rad. Res. Comms. 16: 409-419.