DEVELOPMENTAL CHANGES IN MITOCHONDRIAL FUNCTIONS AND EFFECTS OF CADMIUM TOXICITY ON OXIDATIVE ENERGY METABOLISM.

SUMMARY OF THE
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SUMMARY

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After birth many physiological and biochemical changes take place in th newborn. Enabling it to adapt to its new environment. Many of the regulatory functions previously carried out by the placenta and other maternal organs are quickly assumed by the newborn's organs such as the liver, lungs, kidneys etc. The stage at which each of the organs, their cellular constituents, enzymes etc attain full structural and functional maturity and capacity depends on the type of function that is carried out by the particular organ. Thus liver and the lungs attain full functional capacity much earlier than the brain and the kidneys. The attainment of functional and structural maturity by the mitochondria is an important homeostatic mechanism that aids in the tissue maturity and is necessary for the newborn to maintain an independent existence. The period within which the mitochondria attain maturity is tissue specific, thus liver mitochondria show a sudden surge of activity within hours after birth while at the other end of the spectrum the brain mitochondria, parallel to the pattern of brain growth, gradually attain full capacity.

Although some reports are available on the pattern of developmental changes in the respiratory enzymes, in the fetal, neonatal and perinatal rat liver and brain, not much

information is available on the postnatal development till the adult stage in the other enzymes related to the ETC. In addition, no information is available, especially in case of brain mitochondria, regarding the developmental pattern of the other major constituents of the mitochondrial membrane, the lipids. Hence it was of interest to study the developmental pattern of the rat liver and brain enzymes and lipids from postnatal day 14 to adult stage.

All the enzymes studied, in both the liver as well as brain mitochondria demonstrated a gradual age-dependent increase in activity. The brain oxidative phosphorylation, primary dehydrogenase and ATPase activities in both liver and brain all revealed an increasing trend in activiy. There were some notable exceptions, MDH in brain in contrast to the normal pattern decreased with age, while the GDH in liver decreased between day 21 and 35 and the basal ATPase in brain was the highest on day 21 and then decreased and no stimulation with DNP in any age group was seen in the ATPase activity.

The Km and Vmax of both liver and brain cytochrome oxidase was the highest on day 28 while adults had an intermediate Vmax and a low Km. The SMP ATPase substrate kinetics revealed presence of two catalytic sites, a high affinity and a low affinity site.

The Km in the low affinity site was about 6 to 10 times higher in the corresponding age groups. While the Vmax was

about double. The adults had the lowest Km and an intermediate Vmax. The SMP Arrhenius kinetics showed absence of phase transition in 14- and 35-day groups in liver and 35-day and adult in the brain. The T_t differed by 4.5 ^{o}C in the liver while in the brain there was no change in the groups showing phase transition.

When the developmental pattern of the mitochondrial lipids was studied it was evident that total phospholipid (TPL) content in liver did not differ in any of the age groups while in brain there was a gradual increase till the adults. Cholesterol (CHL) content and TPL/CHL ratio also showed organ- and age-specific variations. The % contribution of TPL and content of the individual phospholipid (PL) classes also changed with age, PC and PE being the major contributors. However, these did not alter much with age although the minor classes increased in content from the initial low amounts to reach the adult values. The liver mitochondrial membrane was found to be more fluid as compared to the brain although there were developmental changes in the pattern.

Thus on the whole the mitochondrial components i.e. enzymes and phospholipids that were studied revealed a tissue-specific pattern with an increasing trend in activity or content with development.

In parallel studies, the effect of cadmium (Cd) on the liver and brain mitochondria, different periods after a single injection to the young and adult rats was checked.

Cd is a major environmental toxicant which has a confirmed role in causing damage to various tissues. Liver is the primary target which is known to accumulate maximum Cd. The damage to liver in terms of cellular destruction is the most studied. Brain on the other hand is maximally protected and at any dose, concentrates only 0.5% Cd as compared to the liver or kidneys which accumulate considerably larger amounts. Mitochondria are known to be a major target of Cd toxicity. However, although the structural damage to mitochondrial membrane and inhibition of a few of the mitochondrial enzymes is reported, no detailed studies on the oxidative phosphorylation and related enzymes is available in either liver or brain in any age group. Hence, in order to obtain this information the effect of Cd on liver and brain mitochondrial enzymes was studied.

In general both liver and brain mitochondria the younger groups seemed to be more resistant to the Cd-insult and the adult and near adult groups showed drastic inhibition of activity of all the enzymes.

The oxidative phosphorylation was stimulated in the young 48 h group while in all the other age groups the activity was inhibited. In case of brain also the young group 2 weeks after Cd injection was relatively unaffected although in all the other groups the activity was impaired. The GDH and MDH in liver and GDH in brain were inhibited in the early stages

after Cd injection, although, later there was not much damage except in the brain GDH activity in young groups 2 months after Cd-treatment, which was further inhibited. SDR, on the other hand, was stimulated in the early periods and later showed impairment in activity.

ATPase activity in the liver was inhibited in all the age groups in both the liver and brain although the degree of inhibition differed depending on the stimulatory condition. Only in case of liver the 48 hr group in the young rats showed stimulated activity. The total -SH content, changed as a consequence of Cd treatment, although this could not be correlated with the effects on enzyme activity. Soluble -SH groups were mostly undetectable.

Thus it can be seen that single exposure of Cd can lead to severe impairment of the mitochondrial fuction and there is no alleviation with passage of time and in fact there is further derangement.