EFFECTS OF CORTICOSTERONE TREATMENT ON MEMBRANE BIOENERGETICS AND STRUCTURE-FUNCTION RELATIONSHIP, IN THE RAT BRAIN.

SUMMARY OF A THESIS

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SUMMARY

Glucocorticoids exert multitude of effects on the nervous system. These effects include control of most basic processes of cellular growth and differentiation, electrophysiological activity and influences on mood, motivation and learned behavioral patterns. Neonatal glucocorticoid administration to rats is known to exert a negative effect on brain growth and development. This includes decrease in brain weight, cell number, content of DNA and protein, thymidine kinase activity and thymidine incorporation into DNA. Glucocorticoid treatment to young rats also suppressed myelination. Development of cortical dendritic spines was retarded with reduction of ganglioside levels in the brain thus interfering with synapse formation.

All the developmental processes involve synthesis of macromolecules like DNA, RNA, proteins and lipids, and would thus be dependent on energy in the form of ATP. It is likely that glucocorticoids could affect the mitochondrial oxidative metabolism and thereby have negative effects on brain development. There are only a few reports on glucocorticoid effect on mitochondrial funtion in brain and these are contradictory. Besides, most of the reported studies were carried out using adult rats and steroids other than corticosterone were used. Steroid hormones play major role in development of brain in the neonatal rats. In view of this it was desirable to examine the effects of corticosterone treatment on mitochondrial funtion and structure-function relationship in

the rat brain during development. Parallel studies were also carried out on liver mitochondria as a model system.

Oxidative energy metabolism of brain mitochondria followed a specific developmental pattern. The effect of *in vivo* corticosterone treatments (acute and chronic) on mitochondrial oxidative energy metabolism were age-dependent and treatment specific. In general both the corticosterone treatments caused significant decrease in state 3 respiration rates and ADP/O ratios, as a result of which the rates of ATP synthesis were lowerd significantly. Animals of 21-and 35-day groups were most affectd by the corticosterone treatments.

Both the corticosterone treatments led to significant decrease in mitochondrial glutamate dehydrogenase and malate dehydrogenase activities. Since mitochondrial primary dehydrogenases form entry points of electrons in mitochondrial electron transport chain, decrease in their activities could be one of the reasons for the observed decrease in state 3 respiration rates. Corticosterone treatment caused significant increase in succinate-DCIP reductase activity but succinate supported mitochondrial state 3 respiration rates remained low in corticosterone treatment groups.

Activity of mitochondrial ATPase, which *in situ* functions towards synthesis of ATP, decreased significantly upon corticosterone treatments to young animals; older animals showed

an increased activity of ATPase in brain mitochondria. Corticosterone treatments also caused significant alterations in Km and Vmax of this enzyme in age-dependent and treatment specific manner. Arrhenius kinetic studies revealed that in 14-day group upon chronic treatment and in 35-day-old adult animals control as well as corticosterone treatment groups, no break was observed in Arrhenius plots of brain SMP ATPase. These changes correlated well with the higher cholesterol content of brain mitochondria from these groups. Both the corticosterone treatments significantly altered the transition temperature and activation energies E_1 and E_2 of brain SMP ATPase.

Many of the mitochondrial enzymes including ATPase have requirement for specific lipid environment for catalytic function. Any alterations in mitochondrial lipids therefore could affet the mitochondrial funtion. Both the corticosterone treatments significantly altered the contents of total phospholipid and cholesterol in brain mitochondria. Effects of corticosterone were more pronounced in young animals than in the adults.

Both the corticosterone treatments induced host of changes in phospholipid content/composition and rates of the synthesis of individual phospholipids of brain mitochondria in age-dependent and treatment-specific manner. As a consequence of these changes, membrane fluidity of brain mitochondria was also altered by the corticosterone treatments.

The resutlts of these studies have clearly shown that corticosterone treatments especially to young rats led to drastic redution in ATP synthesis by brain mitochondria. This could be one of the underlying mechanism for negative effects of glucocorticoid administration on brain development.

Studies on corticosterone effects on liver mitochondria as a model system have shown that effects of this glucocorticoid hormone on mitochondrial structure and function are tissue specific. Corticosterone treatment caused increase in glutamate dehydrogenase activity whereas the malate dehydrogenase activity had decreased significantly. The effects of corticosterone treatments on the activity of succinate - DCIP reductase in liver mitochondria were age-dependent.

Both the corticosterone treatments in general significantly lowered the mitochondrial ATPase activity in the liver. Maximum effects were observed in 21-day-old days. The two corticosterone treatments caused significant alterations in Arrhenius kinetics parameters of liver ATPase. These changes are suggestive of membrane lipid alterations in liver mitochondria.

Corticosterone treatments to rats caused significant increase in total phospholipid content whereas the cholesterol content had decreaed resulting in increase in their molar ratio. Corticosterone content/composition of phospholipids in liver mitochondria and the incorporation of ^{3}H acetate into different

phospholipid classess had decreased.

A rapid, sensitive, specific and economical micromethod for fluorimetric estimation of corticosterone in rat serum, tissues and mitochondria has been developed to examine the levels of corticosterone in the control and the treatment groups.

In control animals, serum corticosterone levels were highest in 7-day group and decreased gradually with advancement of age; brain tissue as well as mitochondria contained 2 to 3 times higher amount of corticosterone compared to the liver. Both the corticosterone treatments caused significant alterations in corticosterone content of serum, brain and liver tissues and mitochondria in age-dependent and treatment-specific manner.