CHAPTER SUMMARIES

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Chapter 1

To evaluate the efficacy of melatonin supplementation therapy (MST) as alternative to ERT in an ovariectomized rat model to assess diabetogenic metabolic dysregulation caused due to estrogen deficiency in post-menopausal individuals. Ovariectomized adult Wistar rats were treated with either estrogen/progesterone, melatonin or a combination of estrogen and melatonin and the rats were provided with food and water *ad libitum*. Body weight gain, feed efficiency, serum glucose, insulin, glucose tolerance and insulin response, serum and tissue lipids, tissue glycogen contents and activities of glycogen phosphorylase and glucose-6-phosphatase were analyzed in all the experimental groups.Ovariectomized animals showed increased body weight gain, feed efficiency, FIRI values, greater AUC for GTT, higher serum and tissue lipids and reduced glycogen contents and insulin sensitivity. Melatonin (low dose) was efficient in reverting all the OVX-induced changes more efficiently than estrogen. Combination of E_2+ML was found to be best in correcting glycaemic dysregulation while, high melatonin (high dose) could effectively regulate dyslipidemia. The present study provides strong evidence for MST to be more potent and effective in comparison to ERT due to its single handed ability to revert all the OVX-induced changes. No reported side/long term effect of melatonin as against the known effects of ERT, makes it a more attractive a candidate to treat post-menopausal symptoms.

Chapter 2

The present study aims to determine the potentials of melatonin supplementation in ameliorating ovariectomy induced oxidative stress. Adult *Wistar* rats were either ovariectomized or sham operated and divided into control (sham operated) and experimental groups respectively. Rats were treated with melatonin, estrogen, progesterone or a combination of melatonin and estrogen for a period of fifteen days. At the end of the treatment period, animals were sacrificed and various parameters of tissue oxidative stress (LPO, GPx, GSH, SOD and CAT), serum markers of renal and hepatic dysfunction (ALP, ACP, SGOT, SGPT, Urea, Creatinine) and serum corticosterone level were evaluated. Ovariectomy induced a significant increase in tissue lipid peroxidation, SGPT, SGOT, ALP, ACP and serum corticosterone titre while a corresponding significant decrement in the levels of enzymatic and non enzymatic antioxidants. Out of the two doses of melatonin employed in the present evaluation, melatonin at a high dose proved capable of reducing ovariectomy induced oxidative stress more effectively than estrogen replacement or even the combination of the two. Overall, Melatonin supplementation therapy qualifies as a potent and safe alternative to ERT in alleviating ovariectomy induced oxidative stress worthy of application to postmenopausal women.

Chapter 3

The present study is designed to evaluate the efficacy of melatonin supplementation as an alternative replacement therapy in estrogen deficient diabetic rats. Ovariectomized diabetic *Wistar* rats were treated with either estrogen/progesterone, melatonin or combination of both estrogen and

melatonin. Various parameters of glucoregulation (serum glucose, insulin, GTT, IRT, tissue glycogen and enzymes of carbohydrate metabolism) and serum and tissue lipids analysed for all the experimental groups indicate melatonin administration singly or in combination with estrogen at a low dose to be most effective in reversing the changes. The higher dose of melatonin was relatively of greater value in regulating dyslipidemia though lower dose was most potent in ameliorating glycaemic dysregulation. The study thereby provides evidence for melatonin as a potential alternative to ERT in estrogen deficient diabetic subjects.

Chapter 4

The present investigation aims at evaluating the role of melatonin supplementation in ameliorating oxidative stress in estrogen deficient diabetic Wistar rats. Ovariectomized adult Wistar rats were made diabetic by alloxan monohydrate administration. These animals were further divided into control and treatment groups where the latter were treated with either melatonin, estrogen/progesterone or a combination of melatonin and estrogen. Various markers of oxidative stress and hepatic and renal dysfunction in serum (Corticosterone, SGPT, SGOT, ALP, ACP, Urea and Creatinine) and tissue (LPO, GSH, GPx, Catalase, SOD and Ascorbic acid) were assessed in all the experimental groups. Results obtained provide compelling evidence for use of a higher dose of melatonin supplementation in alleviating oxidative stress. This ability of melatonin was not only better than Estrogen Replacement Therapy but even more potent than a combination of the two. To conclude, the present evaluation suggests Melatonin Supplementation Therapy as a

safer and effective alternative to Estrogen Replacement Therapy in combating augmented oxidative stress in estrogen deficient diabetic women.

Chapter 5

The present investigation evaluates the long-term plasticity changes induced by neonatal Corticosterone programming on adult metabolic status along with the potential of melatonin in preventing the changes. Healthy male and female Wistar rats were maintained under standard conditions of temperature and light and, when mated females delivered pups, neonates of both sexes were separated and equal number of pups was assigned to lactating mothers. Pups were treated with either saline, corticosterone or a combinational treatment of corticosterone and melatonin from PND 2 to PND 14 and maintained thereafter till 120 days of age. Various serum and tissue parameters pertaining to glycaemic regulation (serum glucose, insulin, GTT, IRT, tissue glycogen and enzymes of carbohydrate metabolism), dyslipidemia (serum and tissue lipids), hepatic and renal distress markers (serum SGPT, SGOT, ALP, ACP, urea and creatinine) and oxidative stress (LPO, GSH, GPx, Catalase, and SOD) were analyzed in adult rats. The results clearly indicate diabetogenic alterations in adults of corticosterone treated rats. These changes include increased fed and fasting glucose levels, increased insulin titres, increased insulin resistance and reduction in insulin sensitivity, dyslipidemia, increased lipid peroxidation and decreased levels of enzymatic and non-enzymatic antioxidants alongwith increment in serum corticosterone titre and elevation in serum markers of hepatic and renal dysfunction. These changes were more pronounced in case of males as compared to females. Melatonin proved as an effective deprogrammer of corticosterone induced

plasticity changes in both the sexes. Overall, it can be concluded that, exposure to corticosterone induces long lasting effects on adult physiology and metabolism, which can be effectively deprogrammed by concurrent treatment with melatonin.

Chapter 6

The present investigation evaluates the long-term plasticity changes induced by neonatal corticosterone programming on adult metabolic status in both males and females. The study also focuses on evaluating the possible role of melatonin as an ameliorating agent in reversing the plasticity changes induced by neonatal corticosterone treatment. Healthy male and female rats were maintained under standard conditions of temperature and light and, when mated females delivered pups, neonates of both sexes were separated and equal number of pups was assigned to lactating mothers. Pups were treated with either saline or corticosterone from PND 2 to PND 14 and, one group of neonatal corticosterone programmed adults was treated with melatonin for 15 days at 120 days of age. Various serum and tissue parameters pertaining to glycaemic regulation (serum glucose, insulin, GTT, IRT, tissue glycogen and enzymes of carbohydrate metabolism), dyslipidemia (serum and tissue lipids), renal and hepatic distress markers (serum SGPT, SGOT, ALP, ACP, urea and creatinine) and oxidative stress (LPO, GSH, GPx, Catalase, and SOD) were analyzed in adult rats. The results obtained clearly indicate neonatal corticosterone programming effect in terms of hyperglycaemia, hyperinsulinemia, increased insulin resistance coupled with reduction in insulin sensitivity, dyslipidemia, increased lipid peroxidation and decreased levels of enzymatic and non-enzymatic antioxidants along with

increment in serum corticosterone titre and elevation in serum markers of hepatic and renal dysfunction. These changes appeared more pronounced in the case of males compared to females. Adult melatonin treatment succeeded in ameliorating the corticosterone induced plasticity changes in terms of bettered glucoregulation and carbohydrate and lipid metabolism but with lesser degree of efficacy in reversing the changes in oxidative stress markers thereby suggesting the need for usage of higher dosage of melatonin for longer duration.

Chapter 7

The present evaluation assesses the thrifty phenotypic response of neonatal corticosterone programming to a diabetogenic challenge in adult rats. The study also explores the role of melatonin in counteracting the effects. Healthy male and female rats were maintained under standard conditions of temperature and light and when mated females delivered pups, neonates of both sexes were separated and equal number of pups was assigned to lactating mothers. Pups were treated with either saline or corticosterone or a combinational treatment of corticosterone and melatonin from PND 2 to PND 14 and maintained thereafter till 120 days of age. At 120 days of age, rats were exposed to a diabetogen (alloxan at a dosage of 120mg/kg) and rats with serum glucose above 300mg/dl were considered diabetic and used for further experimentation. Diabetic rats were treated with saline for a period of 15 days thereafter. Various serum and tissue parameters pertaining to glycaemic regulation (serum glucose, insulin, GTT, IRT, tissue glycogen and enzymes of carbohydrate metabolism), dyslipidemia (serum and tissue lipids), renal and hepatic distress markers (serum SGPT, SGOT, ALP, ACP, urea