Chapter 6 Summary and Conclusions

Summary

The potential effects of endocrine-disrupting compounds (EDCs) on human health in general and reproduction in particular are major concerns among the public and the scientific communities (Damstra, 2003; Andrea *et al.* , 2006). In this regard, already proven reproductive toxicants such as lead and cadmium because of their potential to alter hypothalamic-pituitary-gonadal axis function can rightly be considered as EDCs. Metals have been shown to exhibit either anti-estrogenic/androgenic or estrogenic nature (Suresh and Wang, 2008; Mostafa *et al.* , 2007). The life stages most vulnerable to endocrine disruption are the prenatal and early postnatal periods, because these are the times when organ and neural systems are changing most rapidly (Makoto *et al.*, 2008). It is very well demonstrated that during development the fetus is particularly sensitive to hormonal fluctuations and thereby presence of endocrine disruptors during these periods can more likely interfere in the endocrine signaling that play a very crucial role as far as gonadal maturation and establishment of steroidogenesis capacity of gonads at later stages of life is concerned (Rajapakse *et al.*, 2002; Lise *et al.* , 2006). Exposure to low levels of toxicants may result in permanent physiologic changes that are not seen in adults exposed at similar levels (Bigsby *et al.*, 1999). Hence, the present study is designed so as to analyze the effects of metal exposure during different developmental windows to lead and cadmium either alone or in combination. In this regard, exposure to lead and cadmium (0.05 mg/body wt.) during gestational-lactational window and pubertal window were chosen to analyze the biochemical and molecular mechanism of endocrine disruption across hypothalamic-pituitary-gonadal-hepatic axis. In addition, the biochemical and molecular mechanism of cellular toxicity and increased sensitivity of granulosa cells towards apoptosis mediated by both the metals were also studied.

Pregnant rats were treated subcutaneously (0.05 mg/ kg body wt/day) with lead acetate and cadmium acetate separately and in combination

throughout the **gestational period and** continued even during **the lactational period.** The metal treatment was thereafter withdrawn till post natal day (PND) 55 and all experiments were performed on PND 56 male and female F1 offspring. Frequency of pregnancy was equally distributed over all metal exposure groups and no effect was observed on reproductive performance of the dams. The litter size, pup weights, sex ratio, % mortality, maternal weights did not differ significantly. Since steroid metabolism is under the control of hypothalamic-pituitary axis, it was of interest to know whether early developmental exposure brings about changes at neuroendocrine level in both male and female offspring on reaching adulthood. Hypothalamic dopamine levels decreased in individually and combined metal treated groups in both PND 56 male and female rat offspring. However, norepinephrine levels decreased in individually and combined metal treated groups only in PND 56 male rat offspring whereas in PND 56 female rats, norepinephrine levels decreased only in cadmium treated group. The accumulation of both metals increased in hypothalamus and pituitary after the treatment. Activity of 3α-hydroxy steroid dehydrogenase in hypothalamus and pituitary was decreased after the metal treatment with cadmium showing maximum inhibition in both male and female rat offspring at post natal day 56. Lead exposed rats did not demonstrate any significant decrease in 3α-hydroxy steroid dehydrogenase activity in both male and female rat offspring. From these results it is very clear that there exist sex-specific endocrine disruption at hypothalamic-pituitary axis level. However, the molecular mechanism of endocrine disruption was evaluated only in female offspring. Hypothalamic GnRH mRNA levels were decreased in cadmium and combined treated groups in female rat offspring. Pituitary LH and FSH mRNA levels decreased only in cadmium treated groups in female rat offspring. As these changes were accompanied by increase in metal concentration in both hypothalamus and pituitary it can be suggested that the metal accumulation disrupts the regulatory mechanisms of the hypothalamic-pituitary axis on

reaching adulthood after early developmental exposure to both the metals. One of the possible mechanisms for the metal neurotoxicity is oxidative stress. The antioxidant system of hypothalamus and pituitary in both male and female offspring were susceptible to metal exposure in the present study. Depleted glutathione levels and enhanced lipid peroxidation, a hallmark of oxidative stress was clearly observed in both hypothalamus and pituitary, with maximal effect in the cadmium treated group. However, SOD and CAT enzymes did not demonstrate any significant inhibition in most of the metal treated groups except cadmium treated group, suggesting a adaptive mechanism against the raised amount of production of reactive oxygen species (ROS).The key enzymes of ovarian and testicular steroidogenesis (3β-HSD and 17-βHSD) were affected the most in cadmium and combined treated animals while lead treated animals showed minimum change compared to control group. This decrease in enzymatic activity was correlated to decrease in serum sex-steroid levels. Results also revealed that mRNA levels of genes encoding protein responsible for cholesterol transport and steroidogenesis (StAR, CYP11a), were decreased significantly compared to control in both male and female rat offspring at PND 56. In all treatments, combined treated group showed intermediate results suggesting competition between the two metals. Simultaneous exposure of metal toxicants at this level neither showed any additive effect nor caused clinical signs of toxicity but still able to manifest biochemical and molecular effects affecting the ovarian and testicular function of F1 offspring on reaching adulthood. Cadmium treated animals showed greater effect on cholesterol content compared to other groups. Biochemical effects are correlated with metals accumulated in blood, reproductive tissues like ovary and testis. Histopathological observation of ovary and testis for cytotoxic changes did not demonstrate any marked alterations. However, number of atretic follicles was higher mainly in cadmium exposed group as compared to the control. Hepatic phase-I and phase-II xenobiotic/steroid metabolizing enzymes were inhibited by the metal exposure

in a sex-specific manner. NADPH cytochrome c reductase enzyme activity showed maximal inhibition in cadmium exposed group, whereas combined metal exposed group showed an intermediate effect. Lead exposed group demonstrated the minimal decrease as compared to the control in both male and female rat offspring. Similarly, NADH cytochrome c reductase activity showed maximal inhibition in cadmium treated group with combined group showing an intermediate effect.17β-HSOR and GST enzyme activities exhibited differential pattern of inhibition in liver of male and female rat offspring at PND 56. γ-glutamyl transferase activity also demonstrated maximal inhibition in cadmium treated group whereas combined metal treated group showed an intermediate effect. Interestingly, lead exposed group did not demonstrate any alterations in the enzyme activity in both the sexes. UDP-glucoronyl transferase activity was also inhibited in all the metal treated groups with cadmium showing the maximum inhibition followed by combined metal treatment group. Biomolecules like glycogen, RNA, DNA content were affected in all metal treated groups. Suppressed antioxidant system in liver of both the sexes was observed in the present study. Thus, oxidative stress induced damage is the biochemical basis of endocrine disruption. Toxic parameters like ALP, SGPT and creatinine were altered but were within the normal range. These results are an indication of sex-specific disruption of hepatic bio-transformation enzyme activities and suppressed antioxidant system.

Weaned pre-pubertal rats were treated intraperitonially with lead acetate and cadmium acetate separately and in combination at a dosage of (0.05 mg/ kg body wt/day) from PND 35 till PND 55 **(throughout pubertal developmental window)**. The hypothalamic and pituitary steroid metabolizing enzyme (3α-hydroxy steroid dehydrogenase) activity was significantly inhibited in all the metal exposed groups. Hypothalamic dopamine and norepinephrine content were also significantly decreased in all the metal treated groups as compared to the control. The accumulation of both metals increased in hypothalamus and

pituitary after the treatment. Hypothalamic GnRH mRNA levels were decreased in cadmium and combined treated groups in female rat offspring. Pituitary LH and FSH mRNA levels decreased only in cadmium treated groups. Hypothalamic GSH content was decreased in all the metal treated groups with cadmium exposed group showing maximum decrease as compared to the control. Pituitary GSH content was also decreased in all metal exposed groups with cadmium showing the maximum decrease as compared to the control. Depletion in the reduced glutathione in the metal exposed groups is a hallmark of oxidative injury. Cadmium and combined metal exposed animals showed significant increase in TBARS levels in both hypothalamus and pituitary whereas lead exposed group showed significant increase in TBARS levels as compared to control but was minimal in comparison to other metal treated groups. SOD enzyme activity was inhibited only in pituitary cadmium treated group, but no change was seen in any other metal treated groups in the pituitary. Hypothalamic SOD activity was not inhibited in any of the metal treated groups in both male and female rats. Both male and female rat offspring showed significant decrease in catalase activity only in cadmium treated groups as compared to control in both hypothalamus and pituitary. The key enzymes of ovarian steroidogenesis (3β-HSD and 17-βHSD) were affected the most in cadmium and combined treated animals while lead treated animals showed minimum change compared to control group. This alteration in steroidogenic enzyme activities was followed with decrease in gonadal steroid levels. In all treatments, combined treated group showed intermediate results suggesting competition between the two metals. Simultaneous exposure of metal toxicants at this level neither showed any additive effect nor caused clinical signs of toxicity but still able to manifest biochemical effects and thus affects the ovarian function of pubertally metal exposed animals. Biomolecules like RNA, DNA content were also affected in all metal treated groups. Cadmium treated animals showed greater effect on cholesterol content compared to other groups.

Biochemical effects are correlated with metals accumulated in blood, and ovary. Histopathological observation of ovary for cytotoxic changes demonstrates marked alteration in histology of ovary. Number of atretic follicles was higher mainly in cadmium exposed group as compared to the control whereas the growing follicles were minimum as compared to the control. RT-PCR studies revealed that mRNA expression of genes encoding protein responsible for cholesterol transport and steroidogenesis (StAR, CYP11a, 17β-HSD, 3β-HSD, Aromatase), were decreased significantly compared to control. GSH content was decreased in all the metal exposed groups. Cadmium and combined metal exposed animals showed significant increase in TBARS levels whereas lead treated groups showed the least effect. Antioxidant enzyme activities (CAT, SOD, GSH-Px, and GR) were also significantly suppressed in all the metal exposed groups as compared to the control. Hence, oxidative stress is the underlying biochemical mechanism of endocrine disruption within ovary of post natal day 56 rats after pubertal exposure to metals. Hepatic phase-I and phase-II xenobiotic/steroid metabolizing enzymes studies were inhibited by the metal exposure. NADPH cytochrome c reductase enzyme activity showed maximal inhibition in cadmium exposed group, whereas combined metal exposed group showed an intermediate effect. Lead exposed group demonstrated the minimal decrease as compared to the control. Similarly, NADH cytochrome c reductase activity showed maximal inhibition in cadmium treated group with combined group showing an intermediate effect.17β-HSOR and GST enzyme activities were also significantly inhibited as compared to the control. γ-glutamyl transferase activity also demonstrated maximal inhibition in cadmium treated group whereas combined metal treated group showed an intermediate effect. Interestingly, lead exposed group did not demonstrate any alterations in the enzyme activity. UDP-glucoronyl transferase activity was also inhibited in all the metal treated groups with cadmium showing the maximum inhibition followed by combined metal treatment group. Suppressed antioxidant system was again a

hallmark in metal-induced hepatic toxicity. Toxic parameters like ALP, SGPT and creatinine were altered but were within the normal range.

Further, it was of great interest to examine the potential of a simple method for detecting female reproductive toxicity using ovulation in immature rats induced by exogenous gonadotropins and secondly, to evaluate the underlying biochemical and molecular mechanism of cellular toxicity by lead and cadmium. We thus used luteinized granulose cells as the model system to study the toxic effects of these metals following both *in vivo* and *in vitro* exposure. The suppressed ovulation, following *in vivo* treatment of metals ie from PND 21 to PND 25 and then gonadotropin priming in immature rats, observed in our present study is correlated with altered suppressed steroidogenic enzyme activity, sex steroid production, and increased oxidative stress in the luteinized granulose cells. *In vitro* experiments were performed at a final concentration of 50μM and 200μM of metals. Results on *in vitro* exposure of luteinized granulose cells (from gonadotropin primed immature rats) to Pb and Cd exposure clearly demonstrated altered gonadotropin receptor (LHR and FSHR) mRNA expression, suppressed key steroidogenic enzyme activity (17β hydroxy steroid dehydrogenase) and decreased estradiol and progesterone production in all the experimental groups. Similar change in steroid production was reported earlier by several workers (Paksy *et al.* , 1992; Piasek and Laskey, 1999). Possible reasons for decreased receptor gene expression could be due to metals interference in transcriptional machinery of key receptor genes in granulose cells. Immediate decrease in the activity of 17β-HSD obtained on exposure to Pb and Cd or both can be explained by the binding of metal/s directly to the amino acids present at the active site of the enzyme. Both Pb and Cd can bind to -SH groups of cysteine residue present at the NAD binding domain (Pearson *et al.* , 1991) and thereby altering the structure of the substrate binding site and affecting enzyme function significantly. The study was also designed to understand the granulosa cell's sensitivity towards apoptosis after

metal exposure. Gonadotropins FSH and LH, steroids such as progesterone, and growth factors such as IGF-1, all regulates the 'decision to die' by way of their receptors. Moreover, Bcl-2 family members are major regulators of apoptosis, whereas caspases are the major executioners of apoptotic process. In this regard, the altered expression patterns of IGF-1, FSHR, PR, Bcl and Bax genes are well correlated with the imbalance in sex-steroid production and enhanced oxidative stress.

Conclusions

- Lead and cadmium in isolation and in combination caused significant perturbations in gonadal steroidogenic enzyme activities, decreased sex-steroid levels, decreased mRNA expression of key gonadal steroidogenic proteins and altered gonadal StAR protein expression along with a change in structure of ovary in post natal day 56 F1 generation rats after both gestational-lactational exposure and pubertal exposure regimen. Similar observations were also made in post natal day 56 F1 generation male rats after gestational-lactational exposure regimen.
- Inhibition of steroid metabolizing enzyme activities in hypothalamus, pituitary and liver were observed in post natal day 56 rats after both gestational-lactational and pubertal exposure regimen.
- Decrease in hypothalamic neurotransmitters, pituitary gonadotropin gene expression was observed in post natal day 56 rats after both gestational-lactational and pubertal exposure regimen.
- Based on the presented results, it seemed that oxidative stress due to decreased antioxidant function might occur in post natal day 56 rats after both gestational-lactational and pubertal exposure regimen.
- In order to understand the underlying biochemical and molecular mechanism of cellular toxicity by lead and cadmium, both "in vivo" and

"in vitro" experiments were performed on luteinized granulose cells that showed increased sensitivity of the granulose cells to undergo cell death particularly in cadmium treated group owing to imbalance in sex -steroid production and failure of timely activation of survival and death factors.

Overall, our study demonstrated that Pb and Cd in isolation and in combination brings about neurochemical and neuroendocrine changes, thereby affecting the regulatory role of hypothalamus-pituitary axis on gonadal structure and functions in post natal day 56 rats after being exposed to metals through different developmental windows (prenatal and early post natal). Altered capacity for biotransformation of gonadal steroids in post natal day 56 rats was also evident after early developmental exposure to metals and future studies are necessary to fully understand the sexual dimorphic pattern of endocrine disruption. It can be suggested that combined exposure to metals might not always cause additive or antagonistic effect, but it depends on the duration of the metal exposure, concentration of metal, and most importantly the age during which the metal-exposure have occurred. Elucidation of the mechanisms regulating survival and death of ovarian granulose cells could in the future imply possibilities of interfering with cellular mechanisms involved in pathological conditions such as ovarian infertility, cancer as well as in mechanisms applicable to contraception.

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