6 GENERAL DISCUSSION

The present study demonstrates the effects of BPA on insulin signaling and glucose transport in the testis of rats and the role of reactive oxygen species in mediating the toxic effects of BPA. Following administration with low doses of BPA (0.005, 0.5, 50 and 500 µg/kg/day) for 7 days, the levels of antioxidant enzymes, hydrogen peroxide generation and lipid peroxidation in testis were determined. Exposure to BPA induced oxidative stress in the testis of rats by decreasing the activities of antioxidant enzymes. However, there was no change in the histological architecture of the testis in the BPA-treated rats. Administration with low doses of BPA for 7 days caused an increase in the levels of plasma insulin and estradiol which indicates the endocrine disruptive effects of BPA even at low doses. The activities of glycolytic enzymes in liver increased which signifies that liver responded instantaneously to increased insulin secretion. No changes in the activities of glycolytic enzymes were observed in the testis following BPA administration for 7 days. From the short-term study it was concluded that low doses of BPA induces oxidative stress and hyperinsulinemia, but do not impair histological architecture or glucose homeostasis in the testis of rats.

Persistent hyperinsulinemia has been reported to induce insulin resistance conditions in humans and animal models. In the short-term study, hyperinsulinemia was observed following administration with low doses of BPA and therefore it would be of interest to investigate whether any downstream molecular pathways gets impaired if hyperinsulinemic condition persists. A long-term study with low doses of BPA would provide an ideal platform to study the effects of persistent hyperinsulinemia. Interestingly, we found that long-term (45 days) exposure to BPA at low doses (0.005, 0.5, 50 and 500 µg/kg/day) caused hyperglycemia along with hyperinsulinemia which indicates that BPA caused insulin resistance condition in animals. A decrease in the activities of glycolytic enzymes in testis and liver were observed which signifies impaired glycolysis taking place in these organs. A concomitant increase in oxidative
stress was observed in testis. Since glucose is essential for normal testicular functions, insulin signaling and glucose transport in testis were investigated following BPA administration. A decrease in the levels of insulin and insulin signaling molecules in the testis of rats indicates impairment of insulin signaling pathway following BPA administration. Downregulation of glucose transport as evidenced by decrease in the levels GLUT-2, GLUT-8 proteins and testicular glucose levels signifies that BPA exerts its toxic effects on testis through targeting the glucose transporters. Decrease in the levels of testicular glucose could be one of the possible mechanisms for impaired steroidogenesis in testis as evidenced by decrease in the protein levels of StAR, steroidogenic enzyme activities and plasma testosterone levels. Induction of testicular apoptosis via the activation of extrinsic and intrinsic apoptotic pathways was observed and our results indicate high vulnerability of testis to the toxic effects of BPA.

Molecular docking studies reveal that BPA could directly interact with antioxidant enzymes and decrease their activity. Catalase and glutathione peroxidase were found to have very stable interactions with BPA. The present studies have shown that BPA could directly interact with GLUT-2 and GLUT-8 transporters and pass through the pores and block glucose transport. From the docking studies, it can be concluded that there are similarities in the binding modes of BPA and estradiol with that of cytochalasin B, a known inhibitor of glucose transport. The present study shows for the first time that persistent exposure to BPA at low doses impairs insulin signaling mechanism, glucose homeostasis and steroidogenesis in testis. Oxidative stress and the estrogenicity of BPA contribute to the observed effects. The findings of this study would help in designing strategies for ameliorating the toxic effects of BPA on testis. A model depicting the effects of BPA on insulin signaling and glucose homeostasis has been presented in Fig. 63.
Fig. 63 A model depicting normal testicular functions and its impairment by BPA. The pathway illustrated in the panel A indicates that balanced ROS generation along with normal insulin signaling and glucose homeostasis is essential for testicular spermatogenesis and steroidogenesis. The pathway in the panel B illustrates that during exposure to BPA, increased ROS production along with an increase in the levels of plasma insulin and glucose takes place. This, in turn, would decrease the levels of GLUT-2, GLUT-8 and insulin signaling molecules in testis and thereby contribute to impaired spermatogenesis, steroidogenesis and activates apoptotic pathways in testis. (A high resolution image is available in the enclosed CD.)