6 GENERAL DISCUSSION

The present study demonstrates the effects of nonylphenol (NP) on insulin signaling and glucose transport in the liver of adult male rats and the role of ROS in mediating the toxic effects of NP. Following administration with low doses of NP (15, 150 and 1500 µg/ kg/ day) for 7 days, the levels of antioxidant enzymes, hydrogen peroxide generation and lipid peroxidation in liver were determined. Exposure to NP induces oxidative stress in the liver of rats by decreasing the activities of antioxidant enzymes. Administration with low doses of NP for 7 days caused an increase in the levels of plasma insulin and estradiol, which indicates the endocrine disruptive effects of NP even at low doses. The activities of glycolytic enzymes in liver increased which signifies that liver responded instantaneously to increased insulin secretion. From the short-term study it was concluded that low doses of NP induces oxidative stress and hyperinsulinemia, but do not cause insulin resistance in the liver 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 NP 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 NP would provide an ideal platform to study the effects of persistent hyperinsulinemia. Interestingly, we found that long-term (45 days) exposure to NP at low doses (15, 150 and 1500 µg/ kg/ day) caused hyperglycemia along with hyperinsulinemia which indicates that NP caused insulin resistance condition in animals. A decrease in the activity of glycolytic enzymes in liver was observed which signifies impaired glycolysis taking place in liver. A concomitant increase in oxidative stress was observed in liver. A decrease in the levels of insulin signaling molecules in the liver of rats indicates impairment of insulin signaling pathway following NP administration. Downregulation of glucose transport as evidenced by decrease in the levels of GLUT-2 protein in liver
signifies that NP exerts its toxic effects on liver through targeting the glucose transporters. Induction of hepatic apoptosis via the activation of extrinsic and intrinsic apoptotic pathways were observed and our results indicate high vulnerability of liver to the toxic effects of NP.

Molecular docking studies reveal that NP could directly interact with antioxidant enzymes and decrease their activity. SOD was found to have very stable interactions with NP. The present study shows for the first time that persistent exposure to NP at low doses impairs insulin signaling mechanism, glucose homeostasis and cause oxidative stress and apoptosis in liver. The findings of this study would help in designing strategies for ameliorating the toxic effects of NP on liver. A model depicting the effects of NP on insulin signaling, glucose homeostasis and apoptosis have been presented in Fig. 69.
Fig. 69 Proposed mechanism of action of nonylphenol on liver. The pathway illustrates that exposure to nonylphenol increases ROS production, which down regulate insulin signaling molecules, and thereby decrease glycogen synthesis and increase gluconeogenesis and contribute to insulin resistant in liver. On the other hand nonylphenol-induced ROS activates apoptotic pathways in liver. (A high resolution image is available in the enclosed CD.)