Conclusion

Hypoglycaemia is the major obstacle to optimal blood glucose control in the treatment of diabetic patients. Severe hypoglycaemia triggers a cascade of events in vulnerable neurons that culminate in cell death even after glucose normalization. Our findings demonstrated that glutamatergic system is impaired during hypoglycaemia and diabetes. The evaluations of these damages have important implications in understanding the molecular mechanism underlying cognitive deficits due to intensive insulin treatment in diabetics. Glutamate content increased during hypoglycaemia and diabetes. We observed a prominent significant increase of glutamate content in the brain during hypoglycaemia compared to diabetes. This increased glutamate content caused an increase in glutamatergic function. NMDA receptor subtypes- NMDAR1, NMDA2B and mGluR5 have differential regulatory role in different brain regions and pancreas during hypoglycaemia and diabetes. Dopamine, through DA D2 receptors and glutamate through NMDA receptors regulates insulin secretion. In vitro studies on calcium release using specific antagonist of DA D2 and NMDA receptors have confirmed the role of these receptors in hypoglycaemic and diabetic conditions. The differential functional balance of these receptors control the glucose mediated insulin secretion. The binding parameters of glutamate and NMDA receptors and gene expression studies of NMDAR1, NMDA2B and mGluR5 receptors and GLAST glutamate transporter in diabetic, D+IIH and C+IIH showed a differential functional regulation during hypoglycaemia and diabetes. Hypoglycaemic brain showed an increased glutamate toxicity mediated through NMDA than in diabetic brain. The second messenger study confirmed that the changes in the receptor levels did enhance the IP3, cGMP and cAMP levels. These studies suggest that NMDA receptor potentiates Ca^{2+} release through IP3 receptor activation. Increased Ca^{2+} release is
suggested to trigger release of Cytochrome C thereby initiating the cell damage during hypoglycaemic stress. The behavioural studies by rotarod test show a decrease in motor activity in the hypoglycaemic and diabetic rats with more prominent decrease in hypoglycaemic rats. Thus our results showed that hypoglycaemic condition has more functional damage than diabetic in adult and old rats. It is suggested that the corrective measures for the brain functional damage caused during diabetes and anti-diabetic treatment, through glutamatergic receptors, have therapeutic role in the management of hypoglycaemia and diabetes.