Summary

1. Insulin induced hypoglycaemia and streptozotocin induced diabetic rats were used as models to study alterations in brain dopaminergic function and glutamate receptor gene expression in hypoglycaemia and hyperglycaemia.

2. DA content decreased in the hippocampus, brainstem, cerebral cortex and corpus striatum of diabetic, diabetic+IIH and control+IIH groups with increased HVA/DA turnover rate.

3. Dopaminergic receptor functional status was analysed by Scatchard and displacement analysis using specific [3H]ligands. Receptor binding parameters were confirmed by studying the mRNA status of the corresponding receptor using Real-Time PCR. The total dopamine receptors in hippocampus, brainstem, cerebral cortex and corpus striatum of diabetic+IIH and control+IIH groups increased with decreased affinity. In diabetic group dopamine receptors increased in hippocampus, brainstem and cerebral cortex with decreased affinity whereas it decreased in the cerebral cortex with an increased affinity. Thus, a hyperdopaminergic function with DA depletion observed in different brain regions had a differential effect during hypoglycaemia and hyperglycaemia.

4. Dopamine mediates its action through DA D1 and DA D2 receptors. DA D1 and DA D2 receptors showed increased expression in hippocampus of diabetic, diabetic+IIH and control+IIH. This shows a co-activation of DA D1 and DA D2
receptors with DA depletion in hippocampus affecting DA mediated functions. This co-activation of DA D₁ and DA D₂ receptors should produce opposite or competing intracellular signals through activation of separate DA D₁ and DA D₂ mediated signaling pathways.

5. In brainstem, DA D₁ receptors were up regulated in diabetic, diabetic+IIH and control+IIH groups. DA D₂ receptors decreased in diabetic and diabetic+IIH while it was increased in control+IIH group. Cortical DA D₁ and DA D₂ receptors were up regulated in diabetic, diabetic+IIH and control+IIH group. Corpus striatum of diabetic group showed a decrease of DA D₁ receptors with significant increase in DA D₂ receptors.

6. In diabetic+IIH and control+IIH group, DA D₁ receptors were up regulated with a down regulation of DA D₂ receptors. DA D₁ and DA D₂ receptors have differential regulatory role in different brain regions during hypoglycaemia and hyperglycaemia.

7. Glutamate dehydrogenase activity in the brainstem and cerebral cortex increased in diabetic and diabetic+IIH whereas the activity decreased in control+IIH. MDH activity showed a significant decrease in all the groups compared to control.

8. NMDAR1 receptor gene expression increased in hippocampus, brainstem and cerebral cortex of diabetic+IIH and control+IIH. In diabetic group, NMDAR1 receptor gene expression was increased in hippocampus and brainstem while it was decreased in cerebral cortex and corpus striatum.
9. A prominent brain activity was observed in diabetic+IIH and control+IIH rats compared to diabetic and control by EEG analysis.

10. *In vitro* glucose uptake studies showed that high concentration of DA (10^{-4} M) enhanced glucose uptake by pancreatic islets, while low concentration of DA (10^{-8} M) inhibited glucose uptake during hypoglycaemia and hyperglycaemia. DA D_{2} receptors showed a prominent role on glucose uptake compared to DA D_{1} receptors confirmed by using specific antagonists.

11. *In vitro* glucose uptake studies showed that low concentration of glutamate inhibited glucose uptake while higher concentration stimulated glucose uptake by the islets in hypoglycaemic condition. Glutamate inhibited glucose uptake by pancreatic islets in hyperglycaemic condition. This glutamergic action on glucose uptake by pancreatic islets was mediated through NMDA receptors confirmed by using specific antagonist.

12. *In vitro* insulin secretion studies showed inhibition of insulin secretion in hypoglycaemic condition with maximum inhibition at high concentration of DA. DA D_{1} and DA D_{2} receptors are involved in the DA regulation of insulin secretion during hypoglycaemia where DA D_{2} receptors showed a prominent role as confirmed by using specific antagonist. We observed a significant stimulation of insulin secretion at low concentration of DA and inhibition at high concentration in hyperglycaemic condition. DA D_{1} receptors showed a prominent role in the stimulation of insulin secretion while DA D_{2} receptors in inhibition of insulin secretion confirmed by using specific antagonist.
Our studies showed hypoglycaemic and hyperglycaemic effect on brain function of dopamine through DA D1 and DA D2 receptors, glutamate through NMDA receptors, *in vitro* studies confirming the receptor subtypes functional regulation on glucose uptake and insulin secretion. Thus, it is suggested that the corrective measures for the brain functional damage caused during diabetes and anti-diabetic treatment, through DA D1, DA D2 and glutamergic receptors, have therapeutic role in the management of hypoglycaemia and hyperglycaemia.
Conclusion

Hypoglycaemia is the major obstacle to optimal blood glucose control in 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 dopaminergic system is impaired during hypoglycaemia and hyperglycaemia. The evaluations of these damages have important implications in understanding the molecular mechanism underlying cognitive deficits due to intensive insulin treatment in diabetic patients. DA content decreased during hypoglycaemia and hyperglycaemia. We observed a prominent significant decrease of DA content in the brain during hypoglycaemia compared to hyperglycaemia. This decreased brain DA content caused an increase in dopaminergic function. DA D₁ and DA D₂ receptor subtypes have differential regulatory role in different brain regions during hypoglycaemia and hyperglycaemia. The regional difference in receptor status is relevant to the role that dopamine plays during various physiological and behavioural activities. Dopamine functioning through DA D₁ and DA D₂ receptors regulate insulin secretion. In vitro studies on glucose uptake and insulin secretion using specific antagonist of DA D₁ and DA D₂ receptors have confirmed the role of these receptors in hypoglycaemic and hyperglycaemic conditions. The differential functional balance of these receptors control the glucose mediated insulin secretion. Also, glutamate receptor functional regulation has a control on glucose mediated insulin secretion. The binding parameters of DA D₁ and DA D₂ receptors and gene expression studies of DA D₁, DA D₂ and NMDAR1 receptors in diabetic, diabetic + IIH and control + IIH showed a differential functional regulation during hypoglycaemia and
hyperglycaemia. Hypoglycaemic brain showed an increased glutamate toxicity mediated through NMDA than in hyperglycaemic brain. Thus our results showed that hypoglycaemic condition has more functional damage than hyperglycaemia. The receptor mediated functional studies and in vitro studies using antagonists for the receptor subtypes confirmed the specific receptor mediated dopaminergic and glutamergic brain damage in hypoglycaemia and hyperglycaemia. Thus, it is suggested that the corrective measures for the brain functional damage caused during diabetes and anti-diabetic treatment, through DA D₁, DA D₂ and glutamergic receptors, have therapeutic role in the management of hypoglycaemia and hyperglycaemia.