Conclusion

Diabetes leads to neuronal damage and altered CNS function, making diabetic patients vulnerable to neurodegenerative diseases. The elevated NMDA and AMPA receptors with an alteration in NMDA R1, NMDA 2B, AMPA (GluR2) and AMPA (GluR4) receptor gene expression in the brain regions indicates an impaired glutamatergic receptor function in diabetic condition. The decreased GAD and GLAST mRNA expression in diabetic rats indicates an impairment in glutamate metabolism and transport. The alterations in glutamate metabolism and transport augmented the synaptic glutamate concentration, which resulted in the hyper activation of NMDA and AMPA receptors, thereby leading to glutamate mediated excitotoxicity. The elevated IP3 level in the brain regions of diabetic rats accounts for the Ca\(^{2+}\) mediated toxicity. SOD activity and GPx gene expression were decreased in the brain regions of diabetic rats leading to a state of oxidative stress. Impaired glutamatergic neurotransmission and oxidative stress up regulated the apoptotic factors Bax and caspase 8 and down regulated the anti-apoptotic factor Akt-1 resulting in neuronal death in the brain regions of diabetic rats. The alterations in glutamatergic receptor function, glutamate transporter, glutamate metabolism, IP3 content, antioxidant enzyme function and associated neuronal death were reversed in the brain regions of curcumin and vitamin D\(_3\) treated diabetic rats. In the pancreas of diabetic rats, even though NMDA receptors were not altered significantly, AMPA receptor density, AMPA GluR2 and GluR4 receptor subunit expression were altered. Lowered IP3 content and decreased IP3 receptor expression was observed in the pancreas of diabetic rats. There was an enhanced state of oxidative stress observed in pancreas of diabetic rats through reduced SOD activity and GPx gene expression. In the pancreas of curcumin and vitamin D\(_3\) treated rats, the decreased IP3 content and IP3 receptor expression were reversed. This leads to increased cytosolic Ca\(^{2+}\) concentration, resulting in restored insulin level. Apart from that, vitamin D\(_3\) treatment in diabetic rats reversed the decreased vitamin D\(_3\) receptor resulting in regulation of Ca\(^{2+}\) release in pancreatic β cells. Along with this, the up regulated Pdx1, NeuroD1 and
down regulated Bax and caspase 8 in curcumin and vitamin D₃ treated diabetic rats prevented pancreatic β cell death. The reversed AMPA receptor function and reduced oxidative stress restored insulin secretion. Thus the neuroprotective and anti-diabetic property of curcumin and vitamin D₃ are suggested to have therapeutic role through regulating glutamatergic function in diabetic rats.