SUMMARY AND CONCLUSIONS

It has been observed that even with strict glycemic control, the onset and severity of diabetic complications is not affected. The concept of "metabolic memory," that is of diabetic vascular stresses persisting after glucose normalization, has been supported both in the laboratory and in the clinic in both type 1 and type 2 diabetes (Ceriello et al., 2009; Drzewoski et al., 2009). The mechanisms for propagating metabolic memory appear focused on the nonenzymatic glycation of cellular proteins and lipids and on an excess of cellular reactive oxygen and nitrogen species, in particular originating at the level of glycated mitochondrial proteins and perhaps acting in concert with one another to maintain stress signaling independent of glucose levels (Brownlee, 2005; Ceriello et al., 2009; Drzewoski et al., 2009; Perez-Matute et al., 2009). Therefore, "switching off" the metabolic memory, could be an important strategy for the prevention of diabetic complications.

With this background, the present study was designed to evaluate the impact of tocotrienol, lycopene, sesamol and their combination with insulin on diabetes-induced neuropathic pain and cognitive dysfunction in rats. Moreover, the involvement of oxidative-nitrosative stress and inflammatory cascade in the development of these complications was elucidated.

Chapter 1: Amelioration of Diabetic Neuropathy: Targeting Oxidative-Nitrosative Stress and Inflammatory Cascade

Diabetic neuropathy represents an important complication of diabetes involving a spectrum of structural, functional and biochemical alterations in peripheral nerves. The present study was designed to explore the effect of tocotrienol (25, 50, 100 mg/kg), lycopene (1, 2, 4 mg/kg) and sesamol (2, 4, 8 mg/kg) on neuropathic pain in STZ-induced diabetic rats. Diabetic rats exhibited marked allodynia, hyperalgesia (thermal and mechanical) at 4th week of STZ injection. The enhanced pain sensitivity was accompanied by marked increase in oxidative-nitrosative stress, TNF-α, TGF-β1 and IL-1β.
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release in the serum along with enhanced levels p65 subunit of NFκB and caspase 3 in sciatic nerves of diabetic rats. Co-administration of tocotrienol (25, 50, 100 mg/kg), lycopene (1, 2, 4 mg/kg) and sesamol (2, 4, 8 mg/kg) significantly and dose-dependently prevented various behavioral, biochemical and molecular indices of neuropathic pain associated with diabetes. It was also found that combination of insulin with tocotrienol, lycopene and sesamol showed marked protection of diabetic neuropathy as compared to insulin alone treatment.

Therefore, the major finding of the study is that insulin alone reversed the hyperglycemia but partially reversed the neuropathic pain in diabetic rats. However, insulin in combination with tocotrienol, lycopene and sesamol not only attenuated the diabetic condition but also reversed neuropathic pain by “switching off” the metabolic memory phenomenon through modulation of oxidative-nitrosative stress, inflammatory cytokine release, NF-κB and caspase-3 activity in the diabetic rats and thus these interventions may find clinical application to treat neuropathic pain in the diabetic patients.

Chapter 2: Role of Oxidative-Nitrosative Stress and Inflammatory Cascade in the Development of Diabetes Associated Cognitive Decline

The etiology of diabetes associated cognitive decline is multifactorial and involves insulin receptor downregulation, neuronal apoptosis and glutamatergic neurotransmission. This study was designed to evaluate the role of oxidative-nitrosative stress and inflammatory cascade in diabetes associated cognitive decline and to study the impact of tocotrienol, lycopene, sesamol and their combination with insulin on cognitive function and neuroinflammatory cascade in STZ-induced diabetes. STZ-induced diabetic rats were treated with tocotrienol (25, 50, 100 mg/kg), lycopene (1, 2, 4 mg/kg) and sesamol (2, 4, 8 mg/kg) for 10 weeks. Morris water maze was used for behavioral assessment of memory. Cytoplasmic and nuclear fractions of cerebral cortex and hippocampus were prepared for the quantification of acetylcholinestrase activity, oxidative-nitrosative stress,
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TNF-α, IL-1β, NFκβ and caspase-3. After 10 weeks of STZ injection, the rats produced significant increase in transfer latency which was coupled with enhanced acetylcholinestrase activity, increased oxidative-nitrosative stress, TNF-α, IL-1β, caspase-3 activity and active p65 subunit of NFκβ in different regions of diabetic rat brain. Interestingly, co-administration of tocotrienol (25, 50, 100 mg/kg), lycopene (1, 2, 4 mg/kg) and sesamol (2, 4, 8 mg/kg) significantly and dose-dependently prevented behavioral, biochemical and molecular changes associated with diabetes. Moreover, diabetic rats treated with insulin (10 IU/kg) in combination with tocotrienol (100 mg/kg), lycopene (4 mg/kg) and sesamol (8 mg/kg) produced more pronounced effect on molecular parameters as compared to individual treatments.

Collectively, the data reveals that activation of neuroinflammatory pathway is associated with diabetes induced cognitive impairment and points towards the therapeutic potential of tocotrienol, lycopene and sesamol in diabetic encephalopathy.