Chapter-5

Summary and Conclusions
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The present study investigated the possible role of CB1 receptors in the pathogenesis of diabetes-induced nephropathy. Streptozotocin (STZ) (55 mg/kg, i.p., once) was administered in uninephrectomised rats to induce experimental diabetes mellitus. The oleamide and AM-6545 treatments were started in diabetic rats after 1 week of STZ and were continued for 24 weeks. The development of diabetic nephropathy was assessed biochemically by estimating serum creatinine, blood urea nitrogen, urinary microprotein and urinary albuminuria. In addition, the renal inflammation was assessed by estimating serum levels of tumor necrosis factor-alpha and transforming growth factor-beta. Renal morphological changes were determined by estimating renal hypertrophy and renal collagen content.

On the basis of results of the study, the following salient findings may be summarized.

- In the present study, after 24 weeks, uninephrectomised diabetic rats showed significant renal damage which was assessed in terms of elevated levels of serum creatinine, blood urea nitrogen and elevated urinary levels of microprotein and albumin.

- After 24 weeks, the uninephrectomised diabetic rats showed significant renal morphological changes assessed in terms of increased renal collagen content and renal hypertrophy.

- After 24 weeks, the uninephrectomised diabetic rats showed marked increase in renal inflammation was assessed in terms of increased serum TNF-α and TGF-β.

- Pre-treatment with oleamide (a specific CB1 receptor agonist) for 24 weeks in STZ-induced uninephrectomised rats did not exhibit any significant
effect on diabetes-induced nephropathy as evidenced by results obtained in the study. Treatment with oleamide did not effect the levels of serum creatinine, blood urea nitrogen, urinary microprotein and urinary albumin loss.

- Pre-treatment with oleamide (a specific CB1 receptor agonist) for 24 weeks in STZ-induced uninephrectomised rats exhibited no significant effect on the renal morphological changes as assessed in terms of renal collagen content and renal hypertrophy.

- However, pre-treatment with oleamide (a specific CB1 receptor agonist) for 24 weeks in STZ-induced uninephrectomised rats produced significant detrimental effect on renal inflammation. Administration of oleamide to uninephrectomised diabetic rats showed significant increase in serum levels of tumor necrosis factor-alpha and transforming growth factor-beta.

- Pre-treatment with AM-6545 (a specific CB1 peripheral receptor antagonist) for 24 weeks in diabetic rats significantly attenuated the diabetes-induced nephropathy as assessed in terms of decreased serum creatinine, blood urea nitrogen, urinary microprotein and urinary albumin loss.

- Further, pre-treatment with AM-6545 (a specific CB1 peripheral receptor antagonist) for 24 weeks in diabetic rats significantly attenuated diabetic nephropathy induced morphological changes as evidenced by decrease in renal hypertrophy and renal collagen content.

- In addition, pre-treatment with AM-6545 (a specific CB1 peripheral receptor antagonist) for 24 weeks in diabetic rats attenuated renal
inflammation as assessed in terms of marked decrease in serum levels of tumor necrosis factor-alpha and transforming growth factor-beta.

- In addition, concurrent administration of oleamide and AM-6545 did not produce any significant effect on any of the parameters of diabetic nephropathy, diabetic renal morphological changes and renal inflammation.

Hence on the basis of the above the findings, it may be concluded that diabetic-induced nephropathy may be associated with over expression of CB1 receptors and blockade of CB1 receptors may be beneficial in ameliorating the diabetes-induced nephropathy.