Chapter V

Discussion

The present study shows that plasma concentration of thyroxine was higher in rats given exogenous L-thyroxine for 5 days , while thyroidectomized rats had a lower plasma thyroxine concentration in comparison with the normal rats. Russell's viper venom had no effect on plasma thyroxine concentration in normal , hyperthyroid and hypothyroid rats. During given exogenous L-thyroxine , there was a marked increase in the weight of the kidney . This may be due to the effect of thyroxine on mitosis of cells , since thyroxine - induced hypertrophy in vivo was associated with a rise in mitotic index (Bradley et al., 1974).

Rats given exogenous L-thyroxine had a higher heart rate , mean arterial blood pressure and pulse pressure when compared to normal rats. These results were similar to previous studies (Pronina, 1971 ; Chaiyabutr, 1981 ; Williams, 1981). One of the most distinctive findings in hyperthyroidism is a moderate elevation in systolic blood pressure with little change in diastolic, or a marked increase in pulse pressure. This is often associated with vigorous , brisk and rapid contractions of the heart , which are in contrast with the weak heart beat of hypothyroidism (Tepperman, 1980).

The present study shows that there was significant decreases in heart rate , mean arterial blood presure and pulse pressure while there was

significant increase in renal vascular resistance in hypothyroid rats. These changes were associated with decrease in renal blood flow which were also noted in hypothyroid patients (Woodson et al., 1978) and hypothyroid dogs (Chaiyabutr, 1981 ; Songsataya, 1984). Thus, the decrease in the rate of renal blood flow in hypothyroid rats in the present study should be attribute to the decrease in systemic circulation and the intrarenal vasoconstriction. However, the study by Chaiyabutr (1981) showed that the decrease in the rate of renal blood flow in animal given propylthiouracil could be partitioned that associated with the increase in renal vascular resistance and that caused by local vasoconstriction without the alteration in systemic circulation. The fall in renal blood flow might cause the reduction in glomerular filtration rate accompanying with the increase in plasma concentration of creatinine and urea in hypothyroid rats.

The decrease in hematocrit values indicate a moderate anaemia occurred in rats given the Russell's viper venom. This could be evidence for intravascular hemolysis as has been reported in Russell's viper bited patient (Peiris et al.,1969 ; Chugn et al.,1975 ; Mahasandana et al.,1980).

The present results show that heart rate , mean arterial blood pressure and pulse pressure did not change in normal and hypothyroid rats received the venom injection , while reduction in renal hemodynamic was observed in these groups. The effect of the venom on general circulation and renal hemodynamic in the present study are similar to those of studies in rats (Chaiyabutr et al.,1985) and dogs (Tungthanathanich et al.,1980). They showed that the venom caused an obviously decrease in general circulation

and renal hemodynamic following the initiate of the envenomation. The initiated hypotensive action of the venom has been suggested to be due to prostacyclin (PGI_2) release, causes vasodilation in the periphery, combine with the release of thromboxane A_2 (TXA_2), leukotriene and also histamine from lungs during envenomation an increase in lung perfusion pressure would restrict blood return to heart, and induced hypotensive effect (Huang, 1984 ; Huang et al., 1984). The blood pressure gradually increased and approach the control level within 2 hours. The rise in blood pressure following the transient decrease has been explained by the effect of vasopressive mediator such as renin-angiotensin system (Chaiyabutr et al., 1985). However, renal blood flow and glomerular filtration rate were decreased throughout the period of the experiment. The increase in mean arterial blood pressure with a parallel increase in renal vascular resistance indicates a local vasoconstriction in the kidney. The renin-angiotensin system seem to be responsible for renal vasoconstriction after envenomation since renal blood flow, glomerular filtration rate and urine flow has been shown to increase in envenomated rats after administration of converting enzyme inhibitor (Chaiyabutr et al., 1985). In the present study the effect of renin-angiotensin system may cause decrease in effective renal plasma flow and effective renal blood flow in normal and hypothyroid rats received the venom injection. The reduction of glomerular filtration rate might be related to the fall in renal blood flow. However, in normal rat received the venom injection, the filtration fraction decreased by the reduction of glomerular filtration rate was disproportionate to that of effective renal plasma flow. This result suggests that other factors accounted for the decrease in glomerular filtration rate; since in rats , the reduction of

glomerular filtration rate together with the decrease in hematocrit was due to the decrease in resistance of both afferent and efferent arterioles (Myers et al., 1975).

The reduction of electrolyte excretions , was found to coincide with a decrease in renal blood flow and glomerular filtration rate in normal and hypothyroid rats given the venom.

The present study in hypothyroid rats showed the reduction of plasma sodium, chloride concentrations and arterial blood pressure with the rise in plasma potassium concentration. These changes might expect to cause an increase in rate of renin production and formation of angiotensin II. Angiotensin II would increase adrenal cortical secretion of aldosterone (Guyton,1981). However, the previous report showed that a reduction in renal tubular sensitivity to aldosterone was occurred in hypothyroid rats (Taylor and Fregly, 1964). Therefore, the reduction of plasma sodium and chloride concentration with the rise in plasma potassium concentration would be apparent in the present study. There was a decrease inspite of increase in urinary excretion of sodium and chloride. Since the measurements of these values were carriecd out at only one point in time. Thus, a transient increase in urinary excretion of sodium and chloride probably occurred and caused the reduction in plasma concentration. The reduction of sodium and chloride excretion observed at the time of clearance study could attribute to the decrease in filtered load of sodium and chloride ions.

The apparent of intrarenal vasoconstriction observed in this group may be due to the increase in rate of renal production of renin and of formation of angiotensin II as discussed above. The hypothyroid rats maintained the level of plasma calcium concentration and the rate of urine flow. Thus, the decrease in renal excretion is related to the fall in the filtered load. However , the increase in fractional excretion of calcium was observed in this group. The result may be caused by excessive intake of exogenous calcium gluconate in drinking water.

In normal and hypothyroid rat that received the venom injection have typical features of toxic acute renal injury with the decrease in effective renal blood flow, glomerular filtration rate, while fractional excretion of sodium, potassium, chloride, calcium, and plasma concentration of creatinine and urea were increased. The magnitude of the change was greater in hypothyroid rats. In hyperthyroid rats given the venom injection, the change in effective renal blood flow, glomerular filtration rate, fractional excretion of the electrolytes and plasma concentration of creatinine and urea were not apparent. The study of renal pathological changes showed in good agreement with the physiological study. Glomerular filtration disturbance and vascular lesions were found in both normal and hypothyroid rats received the venom injection. The degree of severity was greater in hypothyroid rats. In hyperthyroid rats received the venom injection, no evidence of glomerular filtration disturbance and vascular lesions were observed.

The studies on hyperthyroid rats showed a tendency to increase in plasma calcium concentration but the significant increase in plasma calcium concentration was noted in hyperthyroid rats that received the venom injection.The changes were similar with hyperthyroid subjects (Krane et al., 1956 ; Baxter and Bondy, 1966). These results may be due to the effect of thyroxine on bone resorption, Since Mundy et al. (1976) demonstrated that prolonged treatment with thyroxine can directly increase bone resorption in cultured fetal rat long bone.

After 24 hours of the venom injection in hyperthyroid rats, the reduction of heart rate and mean arterial blood pressure were apparent. These effects may be related to hypercalcemia which has been shown to cause a slowing of the heart rate in man (Shiner et al., 1969) and inhibition of the renin secretion (Kotchen et al., 1974 ; Watkins et al., 1976). Water diuresis observed in this group may be due to increase in water intake or a diminished response to vasopressin after administration of thyroid hormone (Weston et al, 1956). The increase in plasma chloride concentration showed in this group may be discussed by the state of metabolic acidosis which caused by the reduction of renin-angiotensin-aldosterone system (Guyton,1981).

The present results show that thyroxine will protect against the effect of Russell's viper venom on glomerular and tubular function. Although the chronic administration of thyroid hormone has been shown to increase glomerular filtration rate and decrease fractional excretion of sodium (Katz and Lindheimer, 1973), such effects were not seen in the

saline-injected hyperthyroid rats, but salutary effects were demonstrated in the venom-injected hyperthyroid rats. The protective effect of thyroxine against Russell's viper venom nephrotoxicity may be due to the beneficial effect of high plasma calcium concentration which observed in hyperthyroid rats given the venom injection. Since in vivo experiments showed that hypercalcemia inhibits renin secretion (Kotchen et al.,1974 ; Watkins et al., 1976). The sequence of intracellular events which lead to renal renin release is unknown. Of the factors known to play important stimulatory roles in this process , cAMP (Bondar et al., 1984) and prostaglandins (gerber et al., 1981 ; Henrich, 1981 ; Henrich and Campbell, 1984) have been directly linked to renin release. Most prior studies have demonstrated an inverse relationship between intracellular calcium and renin release in experimental systems (Baumbach and Leyssac, 1977 ; Fynn et al., 1977 ; Park et al., 1981). The study by Henrich and Campbell (1986) implied that changes in intracellular calcium occupy a step that is distal to cAMP-coupled events in the sequence of intracellular events which culminate in renin release.

Recent study suggests that renin-angiotensin system induced renal vesoconstriction after envenomation (Chaiyabutr et al., 1985). The renal vesoconstriction may play a role in the initial pathogenesis of acute renal failure (Schrier and Conger, 1980). In the present study a high plasma calcium concentration in hyperthyroid rats received the venom injection may protect against Russell's viper venom nephrotoxicity.