CHAPTER I

INTRODUCTION

The collecting duct of the mammalian kidney has been known to be responsible for the final regulation of potassium and acid-base excretion via the urine. Changes of transport properties along the collecting duct are considered from the cortical to the inner medullary portion.It has been shown that the first morphologic changes of potassium depletion occur in the intercalated cells of inner stripe of outer medullary collecting duct (OMCDi) which undergo hypertrophy and ultrastructural changes. Secretion of potassium along these tubule segments is sharply curtailed and net reabsorption occur that they are involved on renal potassium adaptation (Wingo, 1989).

The knowledge of potassium adaptive mechanism continues to expand and recent studies help to clarify further the nature of potassium transport and regulation by kidney. Considerable evidence now supports the hypothesis that the kidney possesses a proton and potassium activated adenosine triphosphatase (H-K ATPase) that actively absorbs potassium ions in exchanged for hydrogen ions (Wingo, 1993). The available evidence suggests that the renal H-K ATPase appears identical to the gastric H-K ATPase. It is inhibited by vanadate, omeprazole and Sch28080 and is stimulated by potassium depletion. Potassium depletion would enhance acid secretion by this transporter.The role of the H-K ATPase in collecting duct has been postulated to regulate potassium absorption and cell pH (Kurtzman, 1990).H-K ATPase is localized to the same cell that possess another distinct proton pump, H-ATPase. Both of the proton pumps located in the apical membrane of intercalated cells. The potential role of H-K ATPase in collecting duct on urinary acidification caused the coupling of hydrogen and potassium transport by this pump has been considered. The other proton pump, H-ATPase has been thought to be the major mechanism for luminal acidification in the collecting duct. However, the physiological roles of these two pumps remain controversial, considerable evidence

suggests that H-K ATPase may play an important role in urinary acidification (Wingo, 1993).

It has been shown that aldosterone exert major effect on collecting tubule function (Eiam-ong, Kurtzman,and Sabatini,1991). Aldosterone increases passive potassium secretion and increase H-ATPase activity that associate with potassium wastage and excess acid secretion. While aldosterone deficiency is associated with potassium and acid retention that promote hyperkalemic metabolic acidosis (Kurtzman, 1990).

The excessof aldosterone would stimulate H-ATPase directly in both cortical collecting duct (CCD) and medullary collecting duct (MCD), and further increased acid excretion. Potassium depletion would stimulate the H-K ATPase as well, further enhanced acid excretion. However, potassium depletion alone has been shown to decrease aldosterone release which inhibit the H-ATPase but no affect on H-K ATPase ((Eiam-ong, Kurtzman,and Sabatini,1991). Potassium depletion with aldosterone deficiency affecting on H-K ATPase activity is unclear.

In vitro studies a function of H-K ATPase has been shown that the use of single inhibitor can limit. The appropriated concentrations of a structurally dissimilar inhibitor of the gastric H-K ATPase also inhibit proton and potassium transport. This result provides further evidence that the renal H-K ATPase is structurally similar to gastric H-K ATPase. The specific inhibitor of the gastric H-K ATPase have been developed. The hydrophobic imidazolpyridine, Sch28080 appeared to be more useful and more specific for H-K ATPase than omeprazol which also inhibit N-ethylmaleimide (NEM)sensitive ATPase (Khadouri,et.al, 1991). It has been extensively characterized as a competitive inhibitor of H-K ATPase with respect to potassium. Moreover, this agent does not inhibit H-ATPase (Wingo and Armitage, 1993). However, little data are available on the effect of Sch28080 on renal function in vivo studies.

Therefore, the purpose of this study was to clarify whether the in vivo effect of selective H-K ATPase inhibitor (Sch28080) can change renal hemodynamics and renal acid excretion in hypokalemic dogs.