CHAPTER II
LITERATURE REVIEWS

2.1 K homeostasis and its physiological functions

2.1.1 K homeostasis

K is the most abundant intracellular cation in all eukaryotic cells. K homeostasis (Figure 2) faces two continuous challenges: the proper internal distribution of K and the maintenance of external K balance. Internal K balance depends on the distribution of K among muscle, bone, liver, and red blood cells (RBC) and extracellular fluid (ECF). External K balance is determined by the rates of K intake (100 meq/day) and urinary (90meq/day) and fecal excretions (10 meq/day) (Giebisch, 1998). As is true for most important homoeostatic mechanisms, extracellular K concentration is maintained by the interplay between two controlling systems. The muscle tissues contain approximately 75% of K in the body and the extracellular fluid contains less than 5%, therefore a small fractional shift from muscle intracellular fluid has a significant impact on extracellular K concentration. The kidneys controls excretion by regulating whether K is passively secreted or actively reabsorbed between the intracellular pools of K and extracellular fluid. (Clausen and Everts, 1989; Giebisch, 1998; McDonough and Thompson, 1996; Sejersted and Sjogaard, 2000; Seldin D, 1989). Both extracellular and intracellular K levels must be closely controlled in vertebrates because their ratio has a prominent role in resting membrane potential and ion gradients which are very important for controlling of many cellular functions including neuromuscular functions, acid-base balance, osmotic pressure as well as water retention of the cells (Parthasarathy, 2007).

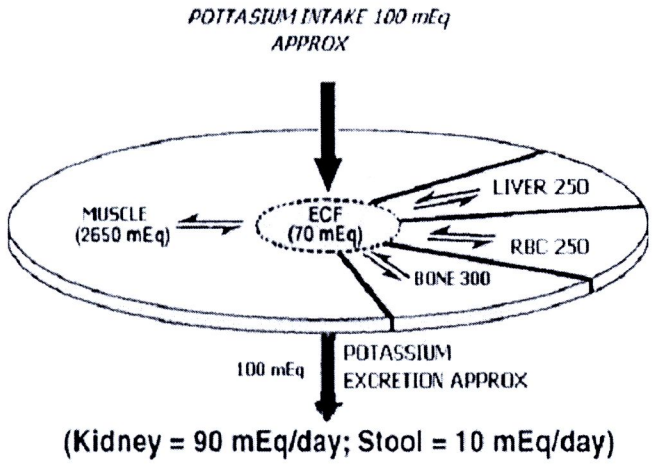

Figure 2 K homeostasis depend on the maintenance of external and internal K balance (Giebisch, 1998)

2.1.2 Physiological roles of K

The principle physiologic roles of K are listed in Table 1. Cellular K contributes the majority of intracellular solutes and thus has a critical role in maintaining normal cell volume. An important relationship also exists between intracellular K and H ion concentrations, such that relatively small changes in the former can greatly perturb intracellular pH, which in turn, regulates including those affecting nucleic acid synthesis and hence protein synthesis and cell growth. The precise maintenance of the K concentration gradient across cell membrane contributes significantly to the resting membrane potential of all cells. It has a crucial role in nerve and muscle excitation. This process involves electrical impulse propagation that is based on rapidly altering the contributions of Na and K electrochemical potential gradients to the cell membrane potential (Parthasarathy, 2007).

Table 1 Physiological roles of K

Roles of intracellular K	**Roles of transcellular K concentration ratio**
Cell volume maintenance (Hazama and Okada, 1988)	Resting cell membrane potential (Kleber, 1983)
Intracellular pH regulation (Bergeron et al., 2003)	Neuromuscular function (Ganetzky and Wu, 1983)
Cell enzyme function (Mujais et al., 1985)	Cardiac pace maker rhythmicity (Vassalle et al., 1964)
DNA/protein synthesis (Canady et al., 1990; Elliott et al., 1986)	
Cell growth (Walsh-Reitz and Toback, 1983)	

2.2 Physiological function of renal cortex and medulla

Renal cortex and medulla serve different functions. Structures in cortex filter fluid and electrolyte from proteins and forms elements, reabsorb glucose, amino acid, water and electrolytes, and produce hormones that modulate blood pressure, hematopoiesis. The medulla is largely responsible for concentrating urine and as a sequence medullary cell must survive in environment where the osmolarity is much higher than the rest of the body. Since various proteins mediated specific function for cortex and medulla, so proteins expression would differ between cortex and medulla (Arthur et al., 2002) as shown in Table 2.

Table 2 Differentially expressed proteins in renal cortex and medulla

Cortex predominant proteins	Medulla predominant proteins
3 Mercaptopyruvate sulfurtranferase	Aflatoxin B1 aldehyde reductase
Alpha 2u globulin	BH3 interacting domain death agonist
Alpha enolase	Glucose regulated protein precursor
Aldehyde dehydrogenase	Fatty acid binding protein
Contraception associated protein 1	Alpha B crystallin
Heat shock protein 60	Albumin
Isocitrate dehydrogenase	
NADH ubiqinone oxidoreductase	
Orthinine aminotranferase	
Retinol binding protein	

(Arthur et al., 2002)

2.3 Renal K transport

The kidney's major role in K homeostasis depends on its ability to respond effectively to changes in external K balance and to stabilize the extracellular concentration of K. The correction of deviations from normal plasma K levels and maintenance of external K balance depend on the intrinsic ability of distal nephron segments to either secrete or reabsorb K. Net K secretion occurs mainly in principal cells while K absorption takes place in intercalated cells (Capasso et al., 1987).

2.3.1 Renal K excretion

The nephron is specific structural unit of the kidney. Its consists of a renal corpuscle and a complicated tubule which is divided into several divisions, such as the proximal, intermediate, and distal tubules. Each division is further subdivided into specific segment as proximal convolutes and straight tubules. A simple scheme to show the nephron with the collecting duct system is illustrated in Figure 3, which is in conformity to the standard nomenclature for the nephron recommended by the Renal Commission Of International Union of Physiological Sciences in 1988 (Kriz and Bankir, 1988).

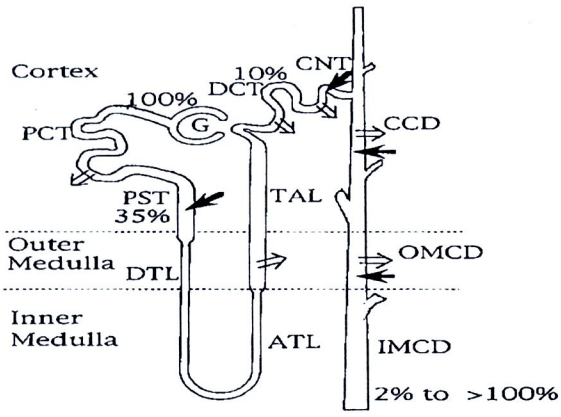

Figure 3 K transport along nephron and collecting duct. G, glomerulus; PCT, proximal tubule, ATL; ascending thin limb, TAL; thick ascending limb; DCT, distal convoluted tubule; CNT, connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct and IMCD; inner medullary collecting duct. Open and filled arrows indicate reabsorption and secretion of K, respectively. Value (%) represent percent of K filtered at glomeruli (Kriz and Bankir, 1988)

2.3.2 Reabsorption of filtered K (Sterns et al., 1981)

Glomerulus. K is a small cation and is not bound in any appreciable amount to plasma protein. The filtered load of K is then plasma multiplied by the glomerular filtration rate (180 l/day), or 720 meq/day.

Proximal tubule. The proximal tubule (convoluted and straight) reabsorbs roughly 80% of the filtered load of K. This fraction remains relatively constant not normally cotribute significantly to the regulation of urinay K excretion.

Loop of Henle. Approximately 10% of the filtered load of K is reabsorbed by the thick ascending limb of Henle's loop. Under normal conditions, the reabsorption of K is relatively constant, although this segment does have the capacity increase K absorption in response to an increase load.

2.3.3 Secretion of K

Distal tubule and collecting duct. It is the distal convoluted tubule and the cortical portion of the collecting duct. The more terminal portions of collecting duct can affect minor adjustments in urinary K excretion. Under most conditions, K is secreted at these sites. However, with K depletion reabsorption of K occurs. These two transport mechanisms are located in separate cells. The secretory cell is the "principal cell," whereas the "intercalated cell" is the cell responsible for K reabsorption.

2.4 Definition of K depletion

K depletion defined as inadequate K intake and hence K levels in the blood are abnormally low. This state is termed **"hypokalemia"**. The most acceptable method to access K status is the determination of total body K content. The technique frequently used for evaluating total body K is the tissue analysis of K content, i.e. quantity per unit tissue. Skeletal muscle, which contains approximately 75 % of body K is commonly used for this purpose (Clausen and Everts, 1989). K depletion is widely defined as muscle K content less than 80 μmol/g wet weight (Dorup et al., 1988).

2.5 Causes of K depletion

2.5.1 Non-renal K loss

The second mechanism for the development of K depletion is the loss of K by other routes than kidney, especially in sweat. When K is lost via an extrarenal route, the kidney usually responds appropriately in an attempt to minimize renal K loss (Tannen et al., 1996). Excessive sweating for the people in the field, particularly for those living in tropical countries, is another main route of K loss. K loss through sweat in the cold and the hot seasons were as high as a third (7.4±2.4 mmol/day) and half (11.5±1.6 mmol/day), respectively, of the urinary excretion (23.25±9.77 and 23.01±9.88 mmol/day) in the cold and hot seasons, respectively) (Sriboonlue et al., 1998a).

2.5.2 Renal K loss

The most common cause of K depletion is the excessive of renal K loss. Renal K loss can be due to drug (thiazide diuretics, loop diuretics, osmotic diuretics), hormone (aldosterone, glucocorticoid-remediable hypertension), bicarbonaturia (distal renal tubular acidosis, correction phase of metabolic alkalosis), magnesium deficiency (other less common causes; cisplatin, toluene), intrinsic renal transport defects (Batter's syndrome, Gitelman's syndrome, Liddle's syndrome)(Weiner and Wingo, 1997). If total body K is depleted, urinary excretion of K will decrease due to increased renal reabsorption (Giebisch, 1998) and the level of K in the urine of all K depletion subjects are below the normal level or hypokaiuria. Sriboonlue et al studied the level of urinary K in 93 healthy rural northeastern Thais males in all there season. The results showed that 76.71%, 90.71% and 81.02% of the sweating were categorized as hypokaliuria (<30 mmol/day) in the hot, rainy and cold seasons, respectively (Sriboonlue et al., 1998a).

2.5.3 Decreased K intake

Low dietary K intake in northeastern Thais is the primary cause of the depletion of K body stores. The assessment of K intake among dwellers in northeastern Thai population clearly showed that their intake were lower than that of the estimated safe and adequate daily dietary intake (ESADI) of the K for the westerners (1975–5625 mg/day), i.e. the mean of K intake in the hot, rainy, and cold seasons were only 807±172, 877± 257 and 902±227 mg/day, respectively (Sriboonlue et al., 1998a). Low K intake in this rural area due to the consume traditional foods, which are of low K compositions (Sriboonlue et al., 1998b).

2.6 The clinical manifestation of K depletion and its effects on kidney

2.6.1 The clinical manifestation of K depletion

K depletion can lead to hypokalemia, which is widely defined as a serum K of less than 3.5 mmol/L. Hypokalemia is one of the most common electrolyte abnormalities encountered in clinical practice and is found in more than 20% of hospitalized patients (Gennari, 1998). The patients with hypokalemia often no symptoms, when the disorder is mild (serum K 3.0 to 3.5 mmol/ L). With more severe

hypokalemia, nonspecific symptoms, such as generalized weakness, lassitude, and constipation, are more common. When serum K decreases to less than 2.5 mmol/L, and at serum concentrations of less than 2.0 mmol/L, an ascending paralysis can develope, with impairment of respiratory function. The symptom will correlated with the rapidity of the decrease in serum K (Gennari, 1998). The clinical manifestations of K depletion has shown in Table 3.

Table 3 Clinical manifestations of K depletion

Organ affected	Clinical sign
Kidney	Infection of urinary tract, acute renal failure, renal hypertrophy, tubulointerstitial injury (Fourman et al., 1956; Muehrcke and Rosen, 1964 ; Riemenschneider and Bohle, 1983; Amlal et al., 2000)
Blood vessels	Impaired renal angiogenesis (Reungjui et al., 2008)
Metabolism	Metabolic alkalosis, decreased intracellular pH, GFR impairment, increased ammonia production, increased hydrogen ion transporter, increased blood pressure, creatinine slowly decreased, hyponatremia, hypochloremia, polyuria, polydpsia, proteinurea (Relman and Schwartz, 1956; Relman and Schwartz, 1958; Morrison and Gardner, 1963; Schwartz and Relman, 1967; Cremer and Bock, 1977; Riemenschneider and Bohle, 1983; Marples et al., 1996)

2.6.2 The effect of K depletion on kidney

Prolonged K deficiency or K depletion causes substantial morphological changes in kidney ultrastructure both in animal model and humans. In 1987, Tolins et al reported that KD rat kidneys had less histologic evidence of tulointerstitial injury and less deposition of complement components C3 and C5b-9 (Tolins et al., 1987), which is crucial mediator of tubulointerstitial damage and progressive renal failure (Nangaku et al., 2002). More detailed analyses of kidney from chronic K deficiency rats were performed by Suga and his colleagues. The renal histopathological examination of chronic K deficiency rats have shown tubulointerstitial injury. The prominent injury was observed in both the cortex and medulla, where there were atrophy or dilation of tubules with mild interstitial accumulation of mononuclear cells, type III collagen deposition. In addition, in the outer medulla, was also observed the diffuse swelling and hyperplasia of collecting duct epithelial cells. Immunohistologic studies documented the increased expression of osteopontin, a sensitve marker of injuried tubules, which predominant in distal tubules of the outer medulla. While the renal cortex found a striped pattern radiating into cortex from the outer medulla (Suga et al., 2002).

Furthermore, there was abnormal finding observed in the kidney from KD mice, including severe tubular dilation, intratubular deposition of amorphous and laminated materials, intratubular cellular casts, and tubular atrophy (Thongboonkerd et al., 2006). Moreover, chronic K depletion, induced by K restriction diet for 3 weeks, is association with a remarkable hypertrophy of the rat kidney include tubulointerstitial injury with glomeruli preservation (Tolins et al., 1987).

In human, several studies reported that K depletion can induced renal hypertrophy, one can observe the development of interstitial fibrosis, hyperplasia of juxtaglomerular apparatus, sclerotic changes, lymphocytic cellular infiltration (Muehrcke and Rosen, 1964; Cremer and Bock, 1977; Riemenschneider and Bohle, 1983; Torres et al., 1990), cyst formation in the renal medulla (Torres et al., 1990), formation of fluid-or air-filled clear spaces within certain kidney cells, dilation or widening of the proximal tubules and fibrosis, the development of fiber-like tissue, formation of cysts within the kidney (Alpern and Toto, 1990). In addition, Harada

et al have reported that a renal biopsy from case of HN associated with primary Sjögren's syndrome (SS) exhibited tubular degeneration, marked interstitial fibrosis and intense macrophage infiltration (Harada et al., 2005).

Recently, Tavichakorntrakool et al showed that the results from kidney autopsies of KD subjects had vacuolization in the kidney cortex, particularly in proximal renal tubular cells (Tavichakorntrakool et al., 2007) (as shown in Figure 4).

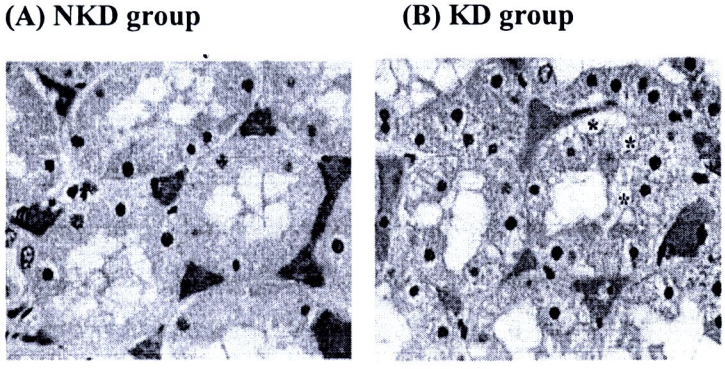

Figure 4 Histopathological examinations of kidney tissues of cadaveric donors. There was vacuolization (marked with*) observed in kidney of KD group (B), but not of NKD group (A). These vacuoles were negative for glycogen and fat stains using Periodic Acid Schiff and Oil Red O, respectively. Original magnification power was 400X in (A) and (B) (Tavichakorntrakool et al., 2007)

2.6.3 The effects of K depletion at cellular level

2.6.3.1 Intracellular pH regulation

K plays important role in variety of cellular functions, including a major regulator of intracellular pH. K depletion can profoundly affect systemic acid-base homeostasis through its effects on multiple components of renal acid-base regulation. Recently, Silver et al showed that K-depleted rats enhanced H^+-ATPase activity at the single intercalated cells (ICs) level, which contributing to the increased H^+ that leading to systemic metabolic alkalosis (Silver et al., 2000).

Additional evidences proposed that K depletion has been related to increased HCO_3^- reabsorption by renal tubules (Nakamura et al., 1998; Amlal et al., 2000). The increasing of HCO_3^- concentration in plasma is associated with the paradoxical excretion of acidic urine (Jones et al., 1982). Moreover, K depletion induced alteration activity of Na^+/K^+ ATPase to absorb NH_4^+ substitute for K, and consequently activated the metabolic alkalosis (Wall et al., 2002; Wall, 2003). In addition, there was studies have provided strong evidence that K-depletion compromises loop of Henle (LOH) function (Luke et al., 1978; Gutsche et al., 1984; Luke et al., 1985; Walter et al., 1988; McKay and Peterson, 1993). There is general agreement that a K-deficiency inhibit sodium and chloride reabsorption (Luke et al., 1978; Gutsche et al., 1984; Luke et al., 1985) and may cause renal chloride wasting by decreasing the number of chloride transporters in renal tubules (Ray et al., 2001). In addition, Morton et al investigated the tandem-pore domain K channel (TSK; K2P channel) families in knockout animals found that to play a role in acid-base homeostasis likewise renal tubular acidosis in human. It is sensitive to change in extracellular pH, especially absorption of $NaHCO_3$ in the proximal tubule has been established (Morton et al., 2005).

2.6.3.2 Apoptosis and cellular volume

Apoptosis is responsible for normal tissue homeostasis and is known to mediate pathological cell loss (Fulton, 1996; Nagata, 1997). Depletion of intracellular K^+ is necessary for cells to shrink, activate caspases and induce DNA fragmentation, events which are features of apoptosis. However, the overall decrease in intracellular K may result not only from the efflux from intracellular K, but also of the inhibition of K uptake resulting from the inhibition of the Na^+/K^+ ATPase, which induced apoptosis of lymphoid cells (Bortner et al., 1997).

Moreover, K depletion results in aquaporin-2 (AQP-2), which is the vasopressin-regulated water channel were decreased in both cortex and medulla induced increase in water permeability of collecting duct is caused by the transfer of water channels from intracellular vesicles to the apical plasma membrane (Nielsen et al., 1995; Sabolic et al., 1995; Marples et al., 1995).

K depletion increase the Na/H exchanger activity in proximal renal tubular cells by the activation of β-subtype-α-adrenergic receptors expression (Muir et al., 1994). In addition, K movements through K channels in the basolateral cell membrane may participate in cell volume regulatory decrease. However, a powerful component of cell volume regulatory decrease in straight proximal tubules of mouse kidney is apparently independent of K conductive pathways, K/H exchanger and Na^+/K^+-ATPase (Volkl and Lang, 1990).

2.6.3.3 Free radical formation factor

Recently several studies reported that K depletion may reflect the decrease of ATP production and led to the failure of Na^+/K^+ pump activity. The Na^+/K^+ pump is highly sensitive to oxidation and free radical formation (Shattock and Matsuura, 1993; Kourie, 1998). The Na^+, K^+, ATPase, some time called Na^+/K^+ pump, is transmembrane enzyme acting as an electrogenic ion transporter in plasma membrane of all memmalian cells. In fact, the Na^+, K^+, ATPase activity extrudes three Na^+ out from the cell, in exchange with movment of two K^+into the cell and utilizes one ATP (Rakowski et al., 1989).

2.6.3.4 Endonuclease activity and endogenous caspase suppression and activation

Recently studies revealed that reduced K^+ concentration is likely a prerequisite for executing a number of apoptic processes, including cell volume decrease, caspase-3 cleavage, cytochrome release, and endonuclease activation (Hughes et al., 1997; Bortner and Cidlowski, 2002). In addition, stimulating K influx using the K_{ATP} channel opener diazoxide either in HL-60 cells resulted in cytochrome *c* release and caspase-3 activation, and all events were blocked by specific channel blocker 5-hydroxydecanoate as well as by overexpression of *bcl-2*, the study showed that *bcl-2* increased to remove of K^+ from mitocondria via the mitocondrial K/H exchanger (Eliseev et al., 2003).

2.6.3.5 Vasomediators activation

K deficiency is associated with a chronic increase in activity of the renin-angiotensin system (RAS). Angiotensin (Ang) II is the main peptide of the RAS as a vasoactive agent that participates in local and systemic hemodynamic regulation (Wolf and Neilson, 1993; Egido, 1996). KD condition likewise the Na/H exchanger inhibition leads to cellular-induced acidosis and subsequently attenuated tubular water absorption, which affects to blood circulation (O'Neil and Hayhurst, 1985).

2.6.4 The pathogenic mechanism of HN

The pathogenesis of HN is considered to be caused by multiple factors. The mechanisms mediating the renal injury include local ischemia and vasoconstriction, intrarenal complement activation and local expression of Ang II. Moreover, HN is associated with alterations in the expression of several growth factor, including insulin-like growth factor-I(IGF-I), insulin-like growth factor biding protein-1 (IGFBP-1), rennin and transforming growth factor-β (TGF-β) synthesis (Whinnery and Kunau, 1979; Linas and Dickmann, 1982; Suga et al., 2002).

The mechanism for Ang II induced tubulointerstitial injury is unclear, but may associate with activation of RAS with intrarenal vasoconstriction, leading to ischemia/or direct stimulating of TGF-β synthesis. Thus, tubulointerstitial damage also results in the loss of peritubular capillaries in association with a decrease in blood flow delivery, which responsible for providing nutrients and oxygen to the tubules. Recent studies from laboratories have described that Ang II infusion strongly stimulates the production and activation of TGF-β in the kidney (Kagami et al., 1994). TGF-β has been shown to be a uniquely powerful fibrogenic cytokine (Border, 1994). TGF-β activated the synthesis of extracellular matrix, to inhibit the actions of protease that degrade matrix. Interestingly, K depletion has been related with increase expression of osteopontin in renal proximal and distal tubules (Malyankar et al., 1997).

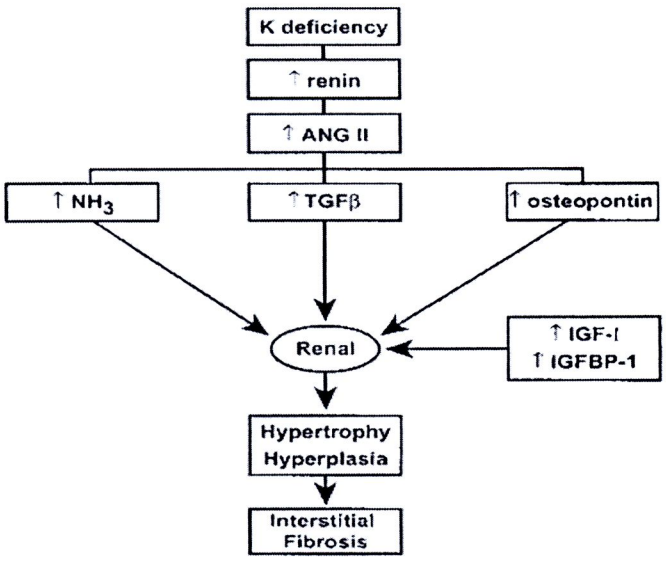

Figure 5 Hypothetical in the pathogenesis of HN
(Fervenza and Rabkin, 2002)

2.7 Proteomic identification in HN

In 2006, Thongboonkerd and his colleagues have applied proteomic technology to discover previously unknown changes in renal proteins expression that are associated with HN. They performed gel-based, differential proteomics analysis of kidneys from BALB/c mice fed with high-normal-K (HNK), low- normal-K (LNK), and K-depleted diet for 8 weeks (n = 6 in each groups). A total of 33 renal proteins were differentially expressed between the KD mice and others, whereas only eight proteins were differentially expressed between the HNK and LNK groups (Figure 6, as determined by quantitative intensity analysis and ANOVA with Tukey's pos hoc multiple comparisons. Using MALDI-MS and/or quadrupole-TOF MS/MS, 30 altered proteins induced by K-depletion were identified as metabolic enzymes (e.g., carbonic anhydrase II, aldose reductase, glutathione *S*-tranferase, GT41A, *etc.*), signaling proteins (14-3-3ε, 14-3-3 ζ, and cofilin 1), and cytoskeletal proteins (γ-actin and tropomyosin).

Some of altered proteins, particulary metabolic enzyme for example, carbonic anhydrase II (CAII) is an ancient ubiquitous enzyme found in every tissues and cell types. CAII is responsible for reversible catalyzing reaction of CO and H_2O to be H^+ and HCO^-_3, acid-base balance, tubular anionic transport and metabolic process at the cellular level (Henry, 1996; Sterling et al., 2001; Tripp et al., 2001). The up-regulation of renal CAII is related, at least in part, to metabolic alkalosis that occurs in HN. Another metabolic enzyme that was significantly altered in HN is aldose reductase. Aldose reductase is an enzyme crucial for the first step of the polyol pathway, of which glucose is converted to sorbitol. Inaddition to catalyzing function in the polyol pathway, aldose reductase involved in the pathogenesis of diabetic complication and myocardial ischemic injury, and may have multiple other activities relating to signal transduction and oxidative defense mechanisms (Hwang et al., 2004; Petrash, 2004). GT41A is one of numerous members of GST-class α that involves in conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles.

The up-regulation of renal GST-class α has been observed in various models of renal tubular injury (Branten et al., 2000; Cressey et al., 2002; Desmots et al., 2002). The up-regulation of GT41A in the KD mice reflect renal tubular injury in HN as renal tubules are the major intrarenal microstructures affected by prolonged hypokalemia. 14-3-3 proteins participate in protein kinase signaling pathways in all eukaryotic cells and play crucial role in regulating multiple cellular process, including initiation and maintenance of cell cycle checkpoints and DNA repairs, prevent apoptosis, and coordination of cell adhesion and cytoskeletal dynamics (Wilker and Yaffe, 2004). The up-regulation of two isoforms of 14-3-3 (ε and ζ) in the KD kidney is still unclear (Thongboonkerd et al., 2006).

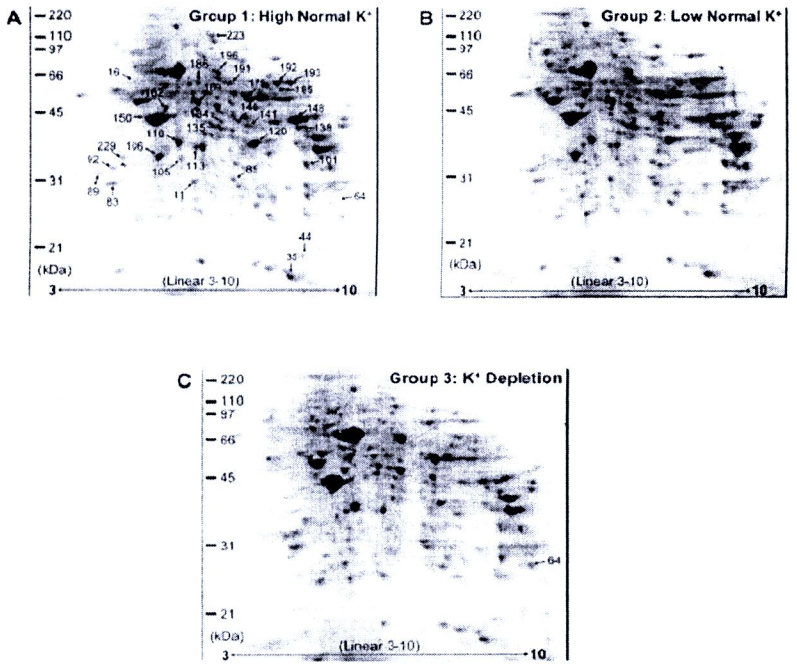

Figure 6 Proteome map of differentially expressed proteins among HNK, LNK and KD groups. Three representative 2-D gels for kidney proteome of the HNK (A), LNK (B) and KD (C) mice. Equal amount of total protein (200 μg) extracted from kidney was loaded in each gel and visualized by Coomassie Brilliant Blue R-250 stain (Thongboonkerd et al., 2006)

2.8 K depletion and common metabolic abnormalities

There are several studies showed that K depletion is related to common metabolic abnormalities. K depletion play roles in citrate metabolism. Low K status causes increase in activities and protein abundance of m-aconitase and cytosolic ATP citrate lyase (ACL). Since m-aconitase and ACL are both citrate-degrading enzyme (ACL is found in cytosolic part of the cell whereas m-aconitase present in mitocondria), increase their activities leads to the decrease in cellular citrate content, hence citrate gradient between intracellular and luminal space increase. Consequently, cellular inward transport of citrate through apical membrane is up regulated. These events will cause the increase in citrate uptake from lumen into cell, and finally result in hypocitrauria (Linas and Dickmann, 1982; Melnick et al., 1998; Melnick et al., 1996),

so that low of citrate leads to high risk of renal stone disease (RSD). Moreover, Silver et al has shown that K depletion increase proton pump (H^+-ATPase) activity in intercalated cell (ICs) of collecting duct from chronically K-depleted rats, which H^+-ATPase residing in the apical membrane of ICs is actively contributing to the increased proton secretion associated with chronic hypokalemia, often leading to systematic metabolic alkalosis. This up-regulation may contribute to the increase H^+ transport that occurs under low-K^+ conditions, and it could also reflect a cellular response involved in maintaining intracellular ion and pH homeostasis in this pathophysiological state (Silver et al., 2000). Furthermore, Wang et al. reported that increased urinary chloride loss in K-depletion (KD) is early event and can lead to hypochoremia, resulting from enhanced chloride loss to has been shown to contribute to maintenance of metabolic alkalosis in hypokalemia (Wang et al., 1997) and subsequently hypovolemia (Luke and Levitin, 1967; Struyvenberg et al., 1965). Inaddition, Berl et al showed that K depletion has an effect on thirst and renal concentrating defect (Berl et al., 1977).

In Northeastern Thailand, K depletion prevails among both healthy and patients with certain metabolic disorders such as renal stone disease (RSD), sudden unexplained death syndrome (SUDS), and distal renal tubular acidosis (dRTA) (Nimmannit et al., 1991; Sitprija et al., 1991; Sriboonlue et al., 1991; Sriboonlue et al., 1993). RSD is a complex, multifactorial disease resulting from environmental and/or genetic interaction. A variety of environmental factors contribute to stone formation i.e., dietary habits, life style, climate and socio-economic status (Sriboonlue et al., 1992; Sriboonlue et al., 1991; Sriboonlue et al., 1993).

Furthermore, RSD may also be associated with hypercalciuria, hyperoxaluria, hypocitrauria, hypokaiuria (Tosukhowong et al., 1991), low urinary pH (Tungsanga et al., 1992). The pathogenesis of these metabolic disorders remains unclear in Northeastern Thailand. It has also been postulated that K depletion is the prime and possibly the most fundamental factor causing a constellation of metabolic disorders associated with hypoklaemia and hypokaliuria, hypocitrauria that are found in the Northeastern Thais (Nimmannit et al., 1991; Sitprija et al., 1991).