CHAPTER I
INTRODUCTION

1.1 Background and rationale of the study

Potassium (K) is the most abundant intracellular cations in all eukaryotic cells and play roles in several cellular functions, and very important to maintain the normal biology and physiology of all cells, tissues, and organs. The muscle and kidney are the main organs responsible for regulation of the normal K balance. While the short-term of K homeostasis occurs via muscle regulation and the long-term depends on renal regulation. However, abnormal K homeostasis may occur when K intake and its output are imbalance. Inadequate dietary K intake, renal K loss (excessive urinary K excretion), and/or extrarenal K loss (*e.g.*, diarrhea and vomiting) can lead to K depletion (or deficiency), which is muscle K content is less than 80 μmol/g wet weight (Dorup et al., 1988).

K depletion (KD) has profound functional consequences in a multitude of organs and systems, of which the most predominantly affected are the hemodynamic, cardiovascular , neurologic, muscular, gastrointestinal, and the renal systems (Antes et al., 1998; Gennari, 1998;Gennari et al., 2000). The kidney defects resulting from chronic K depletion have been defined as "**hypokalemic nephropathy (HK)** ", a disease known for quite some time, but the molecular mechanisms or the links between K deficiency and kidney injury remain unclear (Hollander, 1957; Relman and Schwartz, 1956; Weissmann and Ludwig, 1958). HN is a tubulointerstitial disease that clinically presents as prolonged hypokalemia, polyuria, proteinuria, and progressive loss of renal function and ultimately renal failure or end-stage renal disease (ESRD)(Berl et al., 1977; Kaufman and Kahn, 1988; Suga et al., 2001; Tolins et al., 1987). Even through there are several reports showed that KD was associated with some common metabolic abnormalities such as hypocitrauria, metabolic alkalosis, polyuria, polydipsia , ammoniagenesis, hyponatremia, and hypochloremia (Li et al., 2002; Melnick et al., 1998; Melnick et al., 1996), the pathogenic mechanism of still HN remains unclear.

Recently, Thongboonkerd et al (2006) employed proteomic study to screen the changes in renal proteins expression that are associated with HN in BALC/c mice. The K depleted mice displayed many characteristics of human HN, including severe hypokalemia, polydipsia, marked enlarged kidneys, severe tubular dilation and tubular atrophy. Gel-based, differential proteomics analysis of kidney revealed alterations of several proteins in the K- depleted (KD) mice, as compared to the high-normal- K^+ (HNK) and low-normal K^+ (LNK) animals. These altered proteins play roles in various important cellular functions and may be involved in hypokalemia induced metabolic alkalosis, polyuria, and renal tubular injury, which identified as metabolic enzymes, signaling proteins, and cytoskeletal proteins (Thongboonkerd et al., 2006).

Many evidences have been show that K depletion was the prime and possibly the most fundamental cause associated with some metabolic disorders commonly found among the Northeastern Thai population including renal stone disease (RSD), sudden unexplained death syndrome (SUDS), hypokalemic periodic paralysis (HPP) and distal renal tubular acidosis (dRTA) (Nimmannit et al., 1991; Sitprija et al., 1991; Sriboonlue et al., 1991; Tavichakorntrakool et al., 2007). However, there was no report about the study on the pathogenic mechanism of HN and the linkage between K depletion and HN of the people in this area.

Therefore, this study aim to apply proteomic analysis to explore the expression of renal cortex and medulla proteins in K depletion subjected of Northeastern Thais to get better understanding about the pathogenic mechanism of KD and HN relating with some common metabolic abnormalities found in this region.

1.2 Research questions

1.2.1. What are the differentially expressed proteins in renal cortex and medulla tissues between of the NKD and KD subjects?

1.2.2. How do these altered proteins relate to some common metabolic abnormalities and HN found in northeastern Thais?

1.3 Hypothesis of the study

1.3.1. Proteins were differentially expressed in renal cortex and medulla tissues between of the NKD and KD subjects.

1.3.2. The differentially expressed proteins will provide some informations about metabolic adaptation in renal cortex and medulla of the KD subjects.

1.3.3. The results of these metabolic adaptations will provide some information about K depletion associated with metabolic abnormalities / HN which found in northeastern Thais.

1.4 Objectives of the study

1.4.1. To compare the expression of proteins in renal cortex and medulla tissues between of the NKD and KD subjects.

1.4.2. To identify the differentially expressed proteins in renal cortex and medulla of the NKD and KD subjects.

1.5 Anticipated outcomes

1.5.1. The results from this study will provide informations about the differentially expressed proteins in renal cortex and medulla of the KD subjects.

1.5.2. Our findings will gain some informations about the metabolic adaptation in renal cortex and medulla of KD subjects.

1.5.3. Our findings may explain the pathogenic mechanisms of metabolic abnormalities and HN commonly found in northeastern Thais.

1.6 Scope of the study

The study have applied proteomic analysis to explore the expression of renal cortex and renal medulla proteins. The subjects are divided into two main groups: KD ($K < 80$ μmol/ g wet weight; $n = 6$) and normal or NKD groups ($K \geq 80$ μmol/ g wet weight; $n = 6$).

1.7 Conceptual framework

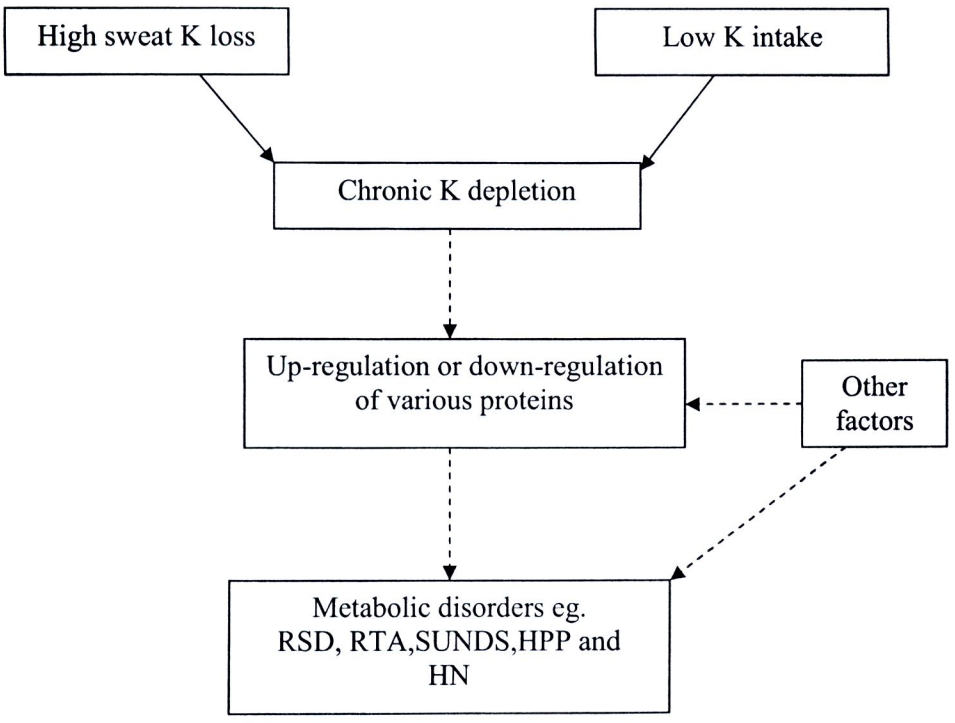

Figure 1 The hypothesis of mechanism K depletion involving in some metabolic abnormalities and HN