Asia-Pacific Journal of Science and Technology: Volume: 22. Issue: 02. Article ID.: APST-22-02-07. Research Article

APST

**Asia-Pacific Journal of Science and Technology**

https://www.tci-thaijo.org/index.php/APST/index

Published by the Faculty of Engineering, Khon Kaen University, Thailand

# Rat model of metabolic syndrome induced by a high-carbohydrate, high-fat diet with fructose in drinking water

Ketmanee Senaphan[1], Upa Kukongviriyapan[1,] *, Poungrat Pakdeechote[1], Veerapol Kukongviriyapan[2], Patchareewan Pannangpetch[2]

[1] Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
[2]Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
*Corresponding author: upa_ku@kku.ac.th

**Abstract**

Metabolic syndrome (MS) is one of the most important challenges to public health and biomedical research. To control this disease, research in rodent models that closely mimic the MS in humans is essential. In this study, a rat model of MS has been developed in male Sprague-Dawley rats by feeding a high-carbohydrate, high-fat (HCHF) diet with 15% fructose solution added to the drinking water. Rats in control group were fed with standard chow diet. During 10 weeks on HCHF diet, rats had developed signs of MS, including hypertension, dyslipidemia, hyperglycemia and impaired glucose tolerance. These alterations were progressively increased throughout 16 weeks of the feeding period. The abdominal fat pads and organ wet weights (heart, liver and kidneys) were significantly increased. Moreover, a significant decrease in hepatic and renal functions was also observed in HCHF diet-fed rats. Overall results suggest that chronic consumption of a HCHF diet by normal rodents provides an adequate rodent model to mimic the human metabolic syndrome. This rat model of MS may be useful for studying the pathophysiological basis of MS in humans and for testing potential therapeutic interventions.

**Keywords**: High-carbohydrate, high-fat diet, Hypertension, Insulin resistance, Dyslipidemia, Metabolic syndrome

## 1. Introduction

The metabolic syndrome is a cluster of metabolic and cardiovascular symptoms that are associated with type 2 diabetes mellitus [1]. The National Cholesterol Education Program: Adult Treatment Panel III (NCEP-ATPIII) definition is one of the most widely used criteria of metabolic syndrome (MS). According to the NCEP-ATPIII definition [2], MS is present if three or more of the following five criteria are met: waist circumference for Asians over 90 cm (men) or 80 (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dL, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women) and fasting blood sugar over 100 mg/dl. Individuals with MS have 2-fold elevated risk of CVD and a 5-fold increased risk of developing diabetes [3]. Furthermore, MS is also associated with an increased risk of nonalcoholic fatty liver disease and kidney dysfunction [4] & [5]. The incidence and prevalence of MS are increasing throughout the world [6] & [7]. In Thailand, the prevalence of MS according to NCEP-ATPIII criteria, with modification of waist circumference (WC) for Asians, is reported to be 32.6% (men 28.7%, women 36.4%) [8]. Therefore, metabolic syndrome is, probably, the most important challenge for health authorities in developed and developing countries [7].

The etiology of MS is complex, both inherited and acquired factors are involved with its background. Numerous animal models have been developed to mimic all major signs of MS in humans, which are genetic-modified, chemically-induced, and diet-induced models [9] & [10]. Although the genetic and chemically-induced models provide useful information on the causes and treatments of MS, they are unlikely to be relevant to the diet-induced human MS [11]. Diet-induced animal models can be used to study the role of unhealthy/unbalanced diet in MS and also to develop other etiological and pathophysiological models. A rat model for MS was established

using a high carbohydrate diet [12]. This model induced hypertension, dyslipidemia, and impaired glucose tolerance but failed to develop central obesity. Meanwhile, using only high-fat diet causes central obesity and dyslipidemia [13]. Therefore, different types of diets may induce MS in a differently way.

It has been reported that a diet high in carbohydrate together with fat mimics the human diet more closely [14]. This combined diet is probably the best model to study human MS. Different combinations and amounts of carbohydrates and fats have been used in different studies [10]. Along with an increased consumption of high-carbohydrate, high-fat diet, there is a rise in consumption of soft drinks and many other sweetened beverages that are high in fructose [15]. Therefore, to mimic unhealthy dietary habits in human, this study was conducted by using a high-carbohydrate, high-fat (HCHF) diet together with 15% fructose in drinking water as beverage. Rats are widely used to mimic human disease states, especially cardiovascular and endocrine diseases [14]. In this study, a rat model of MS has been developed in rats by feeding a HCHF diet with fructose added to the drinking water. Information obtained from this study may help to better understand the pathophysiological changes of this MS model and to develop novel therapies that might slow the progression of this condition in humans.

## 2. Materials and Methods

### *2.1. Preparation of high-carbohydrate, high-fat diet and fructose drinking water*

The composition of HCHF diet and duration of dietary intake have been described in a previous study [14] with some modifications. The HCHF diet was prepared in our laboratory, whereas a standard rat chow was purchased from Chareon Pokapan Company (Bangkok, Thailand). The composition of HCHF diet is shown in Table 1. To prepare 15% fructose solution as drinking water, 15 g of fructose powder was diluted in 100 mL of distilled water. The energy intake of the HCHF diet was 423.21 Kcal/100 g of food and additional 60 Kcal/100 mL of 15% fructose in the drinking water. The energy intake of standard rat chow diet was 386.82 Kcal/100 g of food.

**Table 1** The composition of high-carbohydrate, high-fat diet.

| Composition | HCHF Diet (g/kg food) |
|---|---|
| Fructose | 175 |
| Condensed milk | 350 |
| Powdered rat chow | 200 |
| Pork tallow | 200 |
| Hubble, Mendel and Wakeman salt mixture | 25 |
| Water | 50 |

HCHF; high-carbohydrate, high-fat.

### *2.2. Animals and diets*

Male Sprague-Dawley rats (weighing 220-250g) were obtained from the National Laboratory Animal Center, Mahidol University. All rats were housed in the Northeast Laboratory Animal Center (Khon Kaen University, Khon Kaen, Thailand) under controlled temperature (23 ± 2°C) and humidity conditions and with a 12- h light/dark cycle. Animals were acclimatized for 5 days to the environment with free access to standard chow diet and tab water before experimentation. All experimental protocols were approved by the Animal Ethics Committee of Khon Kaen University (AEKKU/19/2555), under the guidelines of the National Research Council of Thailand.

Rats were randomly divided into 2 groups (n = 10 each); rats in the control group were fed with standard chow diet and tab water as drinking water, whereas rats in the HCHF group were fed with HCHF diet supplemented with 15% fructose in the drinking water. Rats were given *ad libitum* access to food and water. The total feeding time was 16 weeks. Body weight, food and water intakes were measured daily.

### *2.3. Blood pressure measurements*

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were monitored in conscious rats by using non-invasive tail-cuff plethysmography (IITC/Life Science Instrument model 299 and model 179 amplifier; Woodland Hills,CA, USA). Three repeated measurements were taken at each time point for each rat. The average values were then calculated and taken as final readings for SBP, MAP, DBP and HR. All of these parameters were measured every 2 weeks until the end of experimental period.

*2.4. Plasma biochemistry*

Blood samples were collected at the beginning as baseline data, week 10 and week 16 of the feeding protocol. In brief, the animals were fast overnight (12 h). Fructose-supplemented drinking water in HCHF group was replaced with normal water during the food deprivation period. Blood sample was taken from a rat tail vein. Plasma was separated by centrifuging the blood samples at 3500 rpm for 15 min. Fasting blood glucose (FBG) plasma triglycerides (TG) and plasma high-density lipoprotein-cholesterol (HDL-C) concentrations were measured using enzymatic and colorimetric methods (Roche diagnostics, Bangkok, Thailand).

Oral glucose tolerance test (OGTT) was also measured. In brief, after overnight food deprivation, rats were given a glucose load of 2 g/kg BW as 40% glucose solution via oral gavages, and blood glucose concentrations were measured again at 30, 60, 90 and 120 min after administration. The area under the glucose-time course (AUC) was calculated and expressed as mg/dL/120 min.

The liver function was evaluated by measuring plasma alanine transferase (ALT) and alkaline phosphatase (ALP) concentrations using a kinetic rate method [16], [17] & [18]. Moreover, the kidney function was also assessed by measuring the creatinine clearance. Briefly, rats were placed in the metabolic cages for urine 24-h collection. The creatinine concentrations in plasma and urine were measured by automated enzymatic assay [19]. Creatinine clearance (Ccr) was calculated using the standard formula; $UV/P$, where $U$ is the urinary creatinine concentration, $V$ is the 24-h urine volume and $P$ is the plasma creatinine concentration.

*2.5. Organ weights*

At the end of the feeding period, rats were euthanized with pentobarbital sodium (120 mg/kg, i.p.). The blood sample were collected and centrifuged, the plasma was kept at -20°C for biochemical testing. The heart, liver and kidneys were removed and weighed. The retroperitoneal, epididymal, and omental fat were together weighed as abdominal fat. The organ weights were normalized relative to the body weight at the time of their removal and expressed as mg of tissue/g of body weight.

*2.6. Statistical analysis*

All data are presented as mean ± standard error of mean (SEM). Differences between groups were determined by Student's t-test. The time courses of metabolic parameters, kidney and liver function tests for HCHF group were determined using the Paired t-test. $P$ value of $<0.05$ was considered as statistically significant.

**3. Results**

*3.1. Daily intake, body weight and organ weights*

Although mean daily food and water intakes were significantly reduced, HCH diet-fed rats showed higher daily caloric intake compared with control rats fed with standard rat chow ($P<0.05$, Table 2). The body weights of HCHF- and chow-fed rats were not different after 16 weeks (Table 2). However, the abdominal fat pads of HCHF diet-fed rats were significantly increased compared with chow-fed rats ($P<0.05$, Table 2). Increased wet weights of heart, liver and kidneys were found in HCHF diet-fed rats compared with chow-fed rats ($P<0.05$, Table 2).

*3.2. Blood pressure and heart rate*

Figure 1 showed changes in SBP, MAP, DBP and HR of rats fed with HCHF diet for 16 weeks. As shown in Figure 1A and 1B, SBP and MAP were significantly increased after 2 weeks of HCHF feeding, whereas DBP was significantly increased at $4^{th}$ week ($P<0.05$; Figure 1C). Blood pressure was progressively increased throughout 16 weeks compared with those fed with standard chow ($P<0.05$). Moreover, HR of rats fed with HCHF diet also increased after 4 weeks of feeding period ($P<0.05$; Figure 1D).

*3.3. Metabolic parameters*

A significant increase in FBG was found in rats after receiving HCHF diet for 10 and 16 weeks ($P<0.05$; Figure 2A). The AUC values for the OGTTs were significantly increased in HCHF diet-fed rats compared with chow-fed rats ($P<0.05$; Figure 2B), indicating that HCHF diet induced impaired glucose tolerance. Increased TG and decreased HDL-C concentrations were also found in HCHF diet-fed rats ($P<0.05$; Figure 3A and 3B). Overall results suggest that a rat model of MS was achieved after feeding HCHF diet for 16 weeks.

*3.4. Liver enzymes and kidney functions*

To further evaluate whether HCHF diet disturbed the liver and kidney functions, the liver enzymes and kidney Ccr were determined as shown in Figures 4 and 5, respectively. Plasma ALP concentration was significantly increased in rats fed with HCHF diet for 10 weeks rats ($P$<0.05; Figure 4B). After receiving HCHF diet for 16 weeks, both plasma ALT and ALP concentrations were significantly increased ($P$<0.05; Figure 4A and 4B). In addition, Ccr was significantly decreased in HCHF diet-fed rats compared to chow-fed rats ($P$<0.05; Figure 5).

**Table 2** Daily intake, body weight and organ weights in chow-fed and HCHF diet-fed rats.

| Variables | Chow-fed | HCHF |
|---|---|---|
| Food intake (g/day) | 22.63 ± 0.66 | 19.80 ± 0.64* |
| Water intake (mL/day) | 41.13 ± 2.63 | 22.04 ± 1.67* |
| Caloric intake (kJ/day) | 366.22 ± 10.67 | 407.37 ± 9.15* |
| Initial body weight (g) | 240.00 ± 3.69 | 239.65 ± 2.99 |
| Final body weight (g) | 455.93 ± 1.56 | 462.64 ± 7.28 |
| Abdominal fat pads (mg/g body wt) | 38.74 ± 1.65 | 48.34 ± 2.7* |
| Heart wet weight (mg/g body wt) | 2.80 ± 0.01 | 3.17 ± 0.05* |
| Liver wet weight (mg/g body wt) | 27.04 ± 0.65 | 36.37 ± 1.88* |
| Kidney wet weight (mg/g body wt) | 6.20 ± 0.12 | 6.79 ± 0.15* |

Data expressed as mean ± SEM. (N=10/group). * $P$<0.05 vs. chow-fed group.

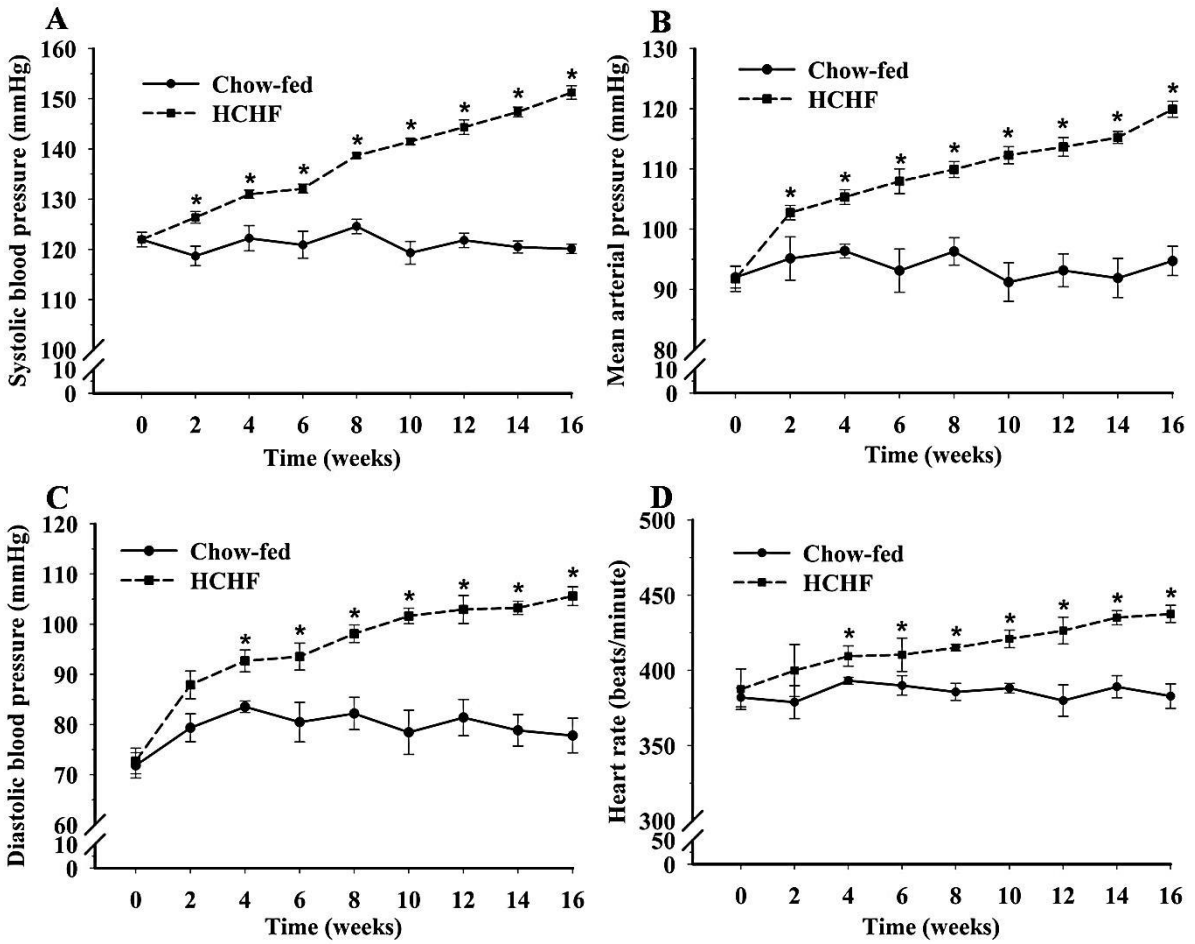


**Figure 1** Changes in systolic blood pressure (A), mean arterial pressure (B), diastolic blood pressure (C) and heart rate (D) during 16 weeks of chow-fed and HCHF diet-fed rats. Data expressed as mean ± SEM. (N=10/group). * $P$<0.05 vs. chow-fed group.

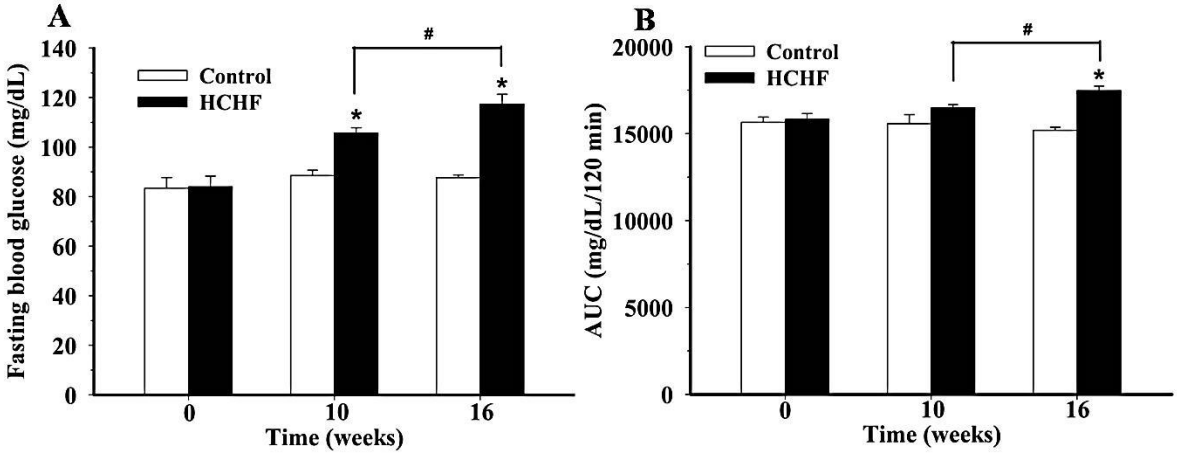


**Figure 2** Changes in fasting blood glucose (A) and AUC (B) in chow-fed and HCHF diet-fed rats. Data expressed as mean ± SEM. (N=10/group). * $P<0.05$ vs. chow-fed group, $^{\#}$ $P<0.05$ vs.10$^{th}$ week of HCHF diet feeding.

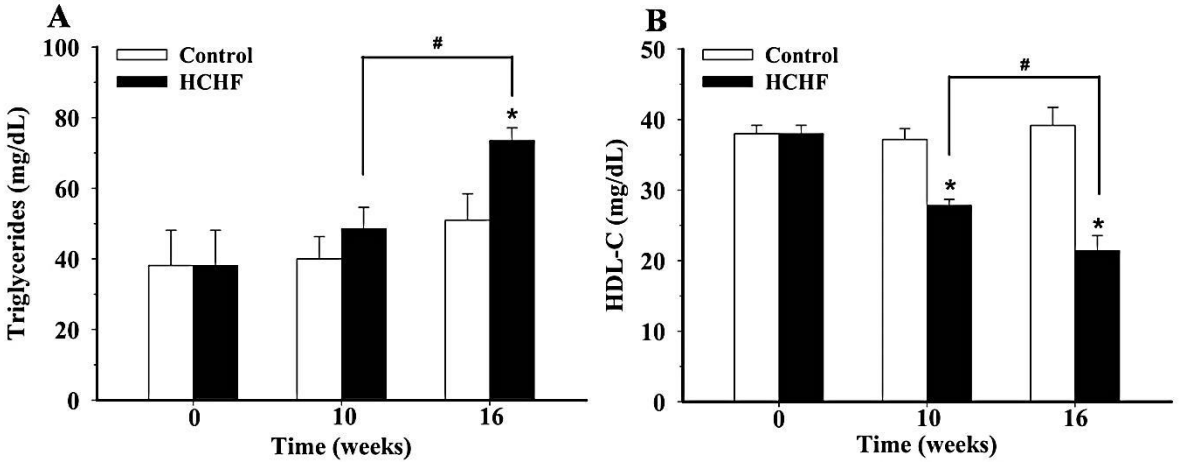


**Figure 3** Changes in plasma triglycerides (A) and HDL-C (B) in chow-fed and HCHF diet-fed rats. Data expressed as mean ± SEM. (N=10/group). * $P<0.05$ vs. chow-fed group, $^{\#}$ $P<0.05$ vs.10$^{th}$ week of HCHF diet feeding.

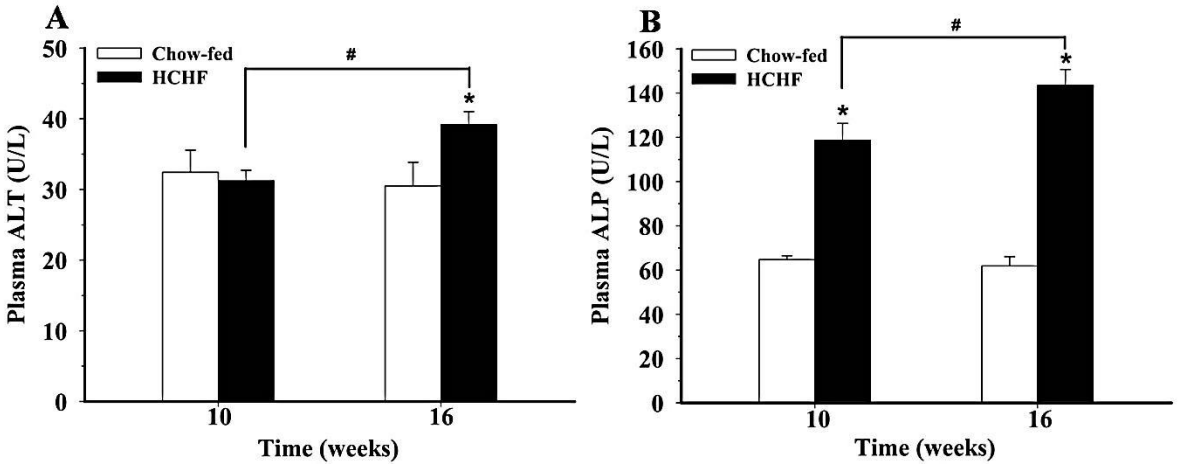


**Figure 4** Changes in plasma ALT (A) and ALP (B) in chow-fed and HCHF diet-fed rats. Data expressed as mean ± SEM. (N=10/group). * $P<0.05$ vs. chow-fed group, $^{\#}$ $P<0.05$ vs.10$^{th}$ week of HCHF diet feeding.

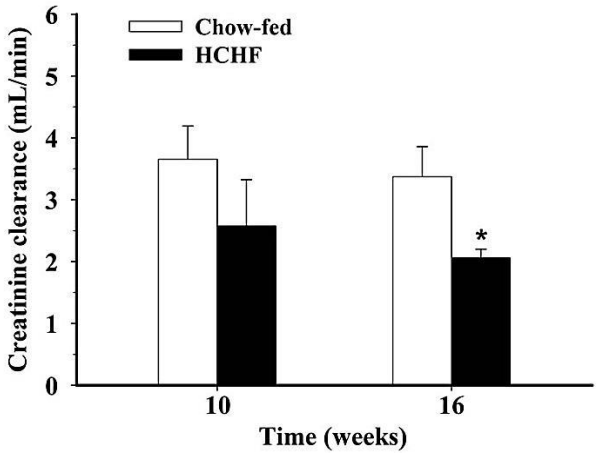


**Figure 5** Change in creatinine clearance in chow-fed and HCHF diet-fed rats. Data expressed as mean ± SEM. (N=10/group). * $P<0.05$ vs. chow-fed group.

**4. Discussion**

MS is a cluster of dangerous factors for cardiovascular diseases, a major cause of mortality in modern society [20]. MS also damages the structure and function of liver, kidneys and pancreas [21]. Therefore, a suitable animal model of MS that mimic all symptoms of human MS is required for evaluating the potential pharmacological interventions to reverse organ dysfunction. To fulfill these requirements, a HCHF diet supplemented with 15% fructose in the drinking water was established in order to induce MS in male Sprague-Dawley rats.

Results of this study showed that rats fed with HCHF diet and 15% fructose in drinking water for 16 weeks developed hypertension, hyperglycemia and dyslipidemia. All of these are the signs of MS [2] & [10]. In this rat model of MS, fat and sugars present in the diet provided more energy than required by the animals. This excess energy is stored in the adipocyte and led to hypertrophy and hyperplasia of adipocytes [22]. Thus, HCHF diet-fed rats displayed increased abdominal fat depositions, and this is an important factor for development of dyslipidemia, hypertension and hyperglycemia [23]. It has been demonstrated that accumulation of visceral adipose tissues increased secretion of adipocytokines, such as leptin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and angiotensinogen [24]. The increased angiotensinogen induced sympathetic over-activity, sodium retention, increased intravascular fluid and vasoconstriction resulting in increased blood pressure [24]. Concurrently, TNF-α stimulated lipolysis, thus promoted free fatty acids (FFA) release into the circulation. The catabolism of FFA by skeletal muscle increased the long chain acylCoA and diacylglycerol levels. These two molecules are known as the powerful allosteric activators of protein kinase C (PKC), which in turn, phosphorylate the insulin receptor substrates-1 (IRS-1) in threonine and serine amino acid residues, thereby induced impairment of insulin signaling pathway resulting in hyperglycemia and insulin resistance [25]. Moreover, a high-flux of fructose to the liver also enhanced rate of *de novo* lipogenesis and triglycerides synthesis, which resulted in dyslipedimia [26]. In consistent with a previous study (14), increased FBG and impaired glucose tolerance were found in rats fed with HCHF diet. The possible mechanism to explain this finding is that insulin sensitivity is reduced with the presence of increased TG [27].

Another component of MS is hypertension, which was developed after consumption of HCHF diet with high fructose drinking water. Several underlying mechanisms involving with hypertension in MS include visceral obesity, insulin resistance, sympathetic overactivity, activated renin-angiotensin system, oxidative stress, endothelial dysfunction and increased inflammation [24] & [28]. In this model, we found insulin resistance, abdominal fat depositions and hypertension in HCHF diet-fed rats. Previous study also found endothelial dysfunction and oxidative stress with hypertension in HCHF diet-fed rats [14].

It has been demonstrated that MS increases risk of non-alcoholic fatty liver disease and kidney dysfunction as previously reported in HCHF diet- [14] and fructose-fed rats [29] & [30]. In agreement with previous reports, we found a decline in hepatic and renal functions after HCHF diet feeding. Previous study in HCHF diet-fed rats found deposition of fat droplets, inflammation and fibrosis in the liver, whereas the kidneys showed glomerular and tubular damage, inflammation and fibrosis [14]. The mechanisms by which HCHF diet induced hepatic and renal dysfunctions are needed for further exploration.

## 5. Conclusion

A HCHF diet with high fructose in drinking water induces MS, hepatic injury and renal dysfunction in male Sprague-Dawley rats. All these changes in this model have mimicked the human metabolic syndrome. This rat model of MS may be useful for testing the pharmacological and other interventions for prevention and treatment of the disease.

## 6. Acknowledgments

This study was supported by grants from the Faculty of Medicine, Khon Kaen University, the Agricultural Research Development Agency and the Thailand Research Fund. Ketmanee Senaphan was supported by a scholarship (PHD/0048/2553) from the Royal Golden Jubilee Ph.D. program, the Thailand Research Fund.

## 7. References

[1] Kendall, D.M., Harmel, A.P., 2002. The metabolic syndrome, type 2 diabetes, and cardiovascular disease: understanding the role of insulin resistance. American journal of managed care 8, S635-653.

[2] American Heart Association, National Heart, Lung, and Blood Institue, Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., Franklin, B.A., Gordon, D.J., Krauss, R.M., Savage, P.J., Smith, S.C., Spertus, J.A., Costa, F., 2005. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. Cardiology in Review 13, 322–327.

[3] Kennedy, A.J., Ellacott, K.L., King, V.L., Hasty, A.H., 2010. Mouse models of the metabolic syndrome. Disease Models & Mechanisms 3, 156-166.

[4] Vanni, E., Bugianesi, E., Kotronen, A., De Minicis, S., Yki-Jarvinen, H., Svegliati-Baroni, G., 2010. From the metabolic syndrome to NAFLD or vice versa? Digestive and Liver Disease. 42, 320-330.

[5] Palanisamy, N., Viswanathan, P., Ravichandran, M.K., Anuradha, C.V., 2010. Renoprotective and blood pressure-lowering effect of dietary soy protein via protein kinase C beta II inhibition in a rat model of metabolic syndrome. Canadian Journal of Physiology and Pharmacology 88, 28-37.

[6] Alberti, K.G.M.M., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.-C., James, W.P.T., Loria, C.M., Smith, S.C., International Diabetes Federation Task Force on Epidemiology and Prevention, Hational Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity, 2009. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120, 1640–1645.

[7] Zimmet, P., Magliano, D., Matsuzawa, Y., Alberti, G., Shaw, J., 2005. The metabolic syndrome: a global public health problem and a new definition. Journal of Atherosclerosis and Thrombosis 12, 295-300.

[8] Aekplakorn, W., Chongsuvivatwong, V., Tatsanavivat, P., Suriyawongpaisal, P., 2011. Prevalence of metabolic syndrome defined by the International Diabetes Federation and National Cholesterol Education Program criteria among Thai adults. Asia Pacific Journal of Public Health 23, 792-800.

[9] Lehnen, A.M., Rodrigues, B., Irigoyen, M.C., De Angelis, K., Schaan, B.D., 2013. Cardiovascular changes in animal models of metabolic syndrome. Journal of Diabetes Research 2013, 761314.

[10] Panchal, S.K., Brown, L., 2011. Rodent models for metabolic syndrome research. Journal of Biomedicine and Biotechnology 2011, 351982.

[11] Marsh, S.A., Dell'italia, L.J., Chatham, J.C., 2009. Interaction of diet and diabetes on cardiovascular function in rats. American Journal of Physiology-Heart and Circulatory Physiology 296, H282-292.

[12] Thirunavukkarasu, V., Anitha Nandhini, A.T., Anuradha, C.V., 2004. Lipoic acid attenuates hypertension and improves insulin sensitivity, kallikrein activity and nitrite levels in high fructose-fed rats. Journal of Comparative Physiology B 174, 587-592.

[13] Buettner, R., Parhofer, K.G., Woenckhaus, M., Wrede, C.E., Kunz-Schughart, L.A., Schölmerich, J., Bollheimer, L.C., 2006. Defining high-fat-diet rat models: metabolic and molecular effects of different fat types. Journal of Molecular Endocrinology 36, 485–501.

[14] Panchal, S.K., Poudyal, H., Iyer, A., Nazer, R., Alam, A., Diwan, V., Kauter, K., Sernia, C., Campbell, F., Ward, L., Gobe, G., Fenning, A., Brown, L., 2011. High-carbohydrate high-fat diet–induced metabolic syndrome and cardiovascular remodeling in rats. Journal of Cardiovascular Pharmacology 57, 51–64.

[15] Bray, G.A., Nielsen, S.J., Popkin, B.M., 2004. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. American Journal of Clinical Nutrition 79, 537-43.

[16] Kamen, A., Wroblewski, F., LaDue, J.E., 1995. Journal of Clinical Investigation 34, 126-33.

[17] Henry, R.J., Chiamori, N., Golub, J., Berkman, S., 1960. Revised spectrophotometric methods for the determination of glutamic oxalacetic transaminase, glutamic pyruvic transaminase and lactic acid dehydrogenase. American Journal of Clinical Pathology 34, 381-398.
[18] Bowers, G.N., McComb, R.B., 1966. A continuous spectrophotometric method for measuring the activity of serum alkaline phosphatase. Clinical Chemistry 12, 70-89.
[19] Junge, W., Wilke, B., Halabi, A., Klein, G., 2004. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffe method. Clinica Chimica Acta 344, 137-148.
[20] Isomaa, B., Almgren, P., Tuomi, T., Forsén, B., Lahti, K., Nissén, M., Taskinen, M.R., Groop, L., 2001. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 24, 683–689.
[21] Musso, G., Gambino, R., Cassader, M., 2010. Non-alcoholic fatty liver disease from pathogenesis to management: an update. Obesity Reviews 11, 430-445.
[22] Jo, J., Gavrilova, O., Pack, S., Jou, W., Mullen, S., Sumner, A.E., Cushman, S.W., Periwal, V., 2009. Hypertrophy and/or Hyperplasia: Dynamics of Adipose Tissue Growth. PLoS computational biology 5, e1000324.
[23] Kershaw, E.E., Flier, J.S., 2004. Adipose tissue as an endocrine organ. The Journal of Clinical Endocrinology & Metabolism 89,2548-2556.
[24] Yanai, H., Tomono, Y., Ito, K., Furutani, N., Yoshida, H., Tada, N., 2008. The underlying mechanisms for development of hypertension in the metabolic syndrome. Nutrition Journal 7, 10.
[25] Gutiérrez-Salmeán, G., Ceballos-Reyes, G., Ramírez-Sánchez, I., n.d. Obesity and metabolic syndrome: Future therapeutics based on novel molecular pathways. Clínica e Investigación en Arteriosclerosis 204–211.
[26] Basciano, H., Federico, L., Adeli, K., 2005. Fructose, insulin resistance, and metabolic dyslipidemia. Nutrition & Metabolism 2, 5.
[27] Paschos, P., Paletas, K., 2009. Non alcoholic fatty liver disease and metabolic syndrome. Hippokratia 13, 9-19.
[28] Tran, L.T., Yuen, V.G., McNeill, J.H., 2009. The fructose-fed rat: a review on the mechanisms of fructose-induced insulin resistance and hypertension. Molecular and Cellular Biochemistry 332, 145-159.
[29] Sánchez-Lozada, L.G., Tapia, E., Bautista-García, P., Soto, V., Avila-Casado, C., Vega-Campos, I.P., Nakagawa, T., Zhao, L., Franco, M., Johnson, R.J., 2008. Effects of febuxostat on metabolic and renal alterations in rats with fructose-induced metabolic syndrome. American Journal of Physiology. Renal Physiology 294, F710-718.
[30] Sánchez-Lozada, L.G., Tapia, E., Jiménez, A., Bautista, P., Cristóbal, M., Nepomuceno, T., Soto, V., Avila-Casado, C., Nakagawa, T., Johnson, R.J., Herrera-Acosta, J., Franco, M., 2007. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. American Journal of Physiology. Renal Physiology 292, F423-429.