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Uricemia in juvenile pigs model: effect of nephrectomy and potassium oxonate

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ABSTRACT. Uric acid is the end product of dietary and endogenous purine metabolism in humans and higher primates. In all lower mammalian species it is converted to allantoin by liver uricase. The aim of this study was to investigate the uric acid turnover in pig model after nephrectomy surgery, fructose-enriched diet and potassium oxonate application. The first experiment was performed using 4 intact control pigs and 8 nephrectomized (5/6 nephrectomy) pigs. Both groups were fed high-fat diet enriched with 20% of fructose for 3 weeks. During the second experiment, as another approach to induce hyperuricemia, potassium oxonate solution (POx) was administered intravenously to 4 healthy pigs, once or twice per day. In the third preliminary experiment one healthy and two nephrectomized (9/10 nephrectomy) pigs were infused with POx to induce hyperuricemia. Results showed that 5/6 nephrecotomy did not affect plasma uric acid concentration for 25 days following surgery. The consumption of the high-fat diet enriched with 20% of fructose did not result in the rise of plasma uric acid, either in healthy or nephrectomized pigs. Administration of POx solution to healthy and 9/10 nephrectomized pigs resulted in significantly increased plasma uric acid concentrations for 18 h and 24 h, respectively, following a single POx infusion. The present study expands today available data on uric acid metabolism in pigs as a model for exploring uricemia in human with kidney dysfunction.

Introduction

Uric acid (UA) is a product of dietary or endogenous purines metabolism, generated by xanthine oxidase/xanthine dehydrogenase, primarily in the liver and intestine (Kang and Nakagawa, 2005). In humans UA is the final end product of purine metabolism, whereas in most mammals it is further degraded into 5-hydroxyisourate by uricase, eventually producing allantoin (Johnson et al., 2013a).

The last one is excreted freely in the urine. In contrast to animals, human tissues have a very limited ability to metabolize urate, which must be eliminated by the kidney and probably by the gut, in order to maintain homeostasis (Terkeltaub, 2010). The kidneys manage UA by multiple and complex processes, including glomerular filtration and reabsorption, secretion, and postsecretory reabsorption in the proximal convoluted tubule. In humans urate transporter, URAT1 (encoded by the *SLC22A12* gene), facilitates UA reabsorption in the proximal convoluted tubule up to 90%, so that the fractional excretion of urate with urine is about 10%. In some mammalian species, particularly in pigs and rabbits, gene *SLC22A12* appeared to be inactivated, and results in much more higher fractional excretion of urate, as compared with human (Jalal et al., 2013; Mandal and Mount, 2015).

Physiological role of UA in the organism is poorly understood. On the one hand, UA is considered to be one of the most important antioxidants in the plasma, which not only protects neuronal cells due to its antioxidant activity, but also plays a role in maintaining blood pressure (Johnson et al., 2008; Mandal and Mount, 2015). On the other hand, UA is poorly soluble in the serum and can precipitate to cause ailments such as gout or urate kidney stones (Terkeltaub, 2010; Lee et al., 2013).

An abnormally high level of blood UA (≥7 mg/dl) is called hyperuricemia and in human can lead to the development of diseases such as hypertension, cardiovascular disorders, diabetes, obesity, hyperlipidemia and cancer (Terkeltaub, 2010; de Oliveira and Burini, 2012). Serum UA levels can be increased by diets high in purine-rich foods or fructose, or by conditions associated with high cell turnover (Johnson et al., 2013a,b). Reduced urinary excretion of UA can also result in higher serum uric acid levels, reduced renal function, reduced renal blood flow and insulin resistance (Ichida et al., 2012; Fathallah-Shaykh and Cramer, 2014).

Although the UA metabolism have been described in many animals, particularly in rodents, dogs, cats, goats and calves (Roch-Ramel and Peters, 1978), little is known about changes in UA turnover in pig under different conditions. Swine model more accurately reflects the changes occurring in humans, not only because of the anatomical similarities but also due to a metabolic rate closer to humans when compared to rodents (Swindle et al., 2012). Therefore, studies of metabolomics and proteomics with this model is a critical step in understanding physiology, pathophysiology and the development of therapies in both humans and animals (Malagrino et al., 2014). In our previous study we investigated the extra-renal elimination of uric acid *via* the intestine in a healthy pig model and the effect of oral uricase therapy on plasma uric acid concentrations in nephrectomized pigs with induced hyperuricemia (Szczurek et al., 2017). Many studies described development of hyperuricemia in human with chronic kidney disease (CKD) and obesity (de Oliveira and Burini, 2012). So, it was hypothesized that 5/6 nephrectomy together with food enriched with fat and fructose could led to the development of hyperuricemia in pig. The main purpose of this study was to describe UA turnover in pigs after nephrectomy surgery, different diet (high-fat diet and fructose) and potassium oxonate application.

Material and methods

Animals

All experimental procedures were approved by the Ethics Review Committee on Animal Experiments of Lund University (Lund, Sweden) and II Local Ethics Committee in Warsaw (No. of approval WAW2/088/2018). In total, nineteen male pigs, castrated within the first week of life, with an average age of 12 ± 2 weeks and a body weight of 16 ± 4 kg at the start of the experiments were used in the present study. The pigs were housed in individual pens equipped with a feeding trough, drinking nipple and constant heating lamp (150 W). Temperature was maintained constant (22 ± 2 °C) and pigs were subjected to a 12/12 h light/dark cycle. During urine sample collections, pigs were housed in metabolic cages under the same conditions. The pigs were allowed to move freely within their pens and metabolic cages, and had visual contact with each other. Throughout the study, the pigs were fed a cereal-based feed (Wytwórnia Pasz 'Morawski', Kcynia, Poland) in an amount of 4% of their body weight per day.

Surgery

The pigs were fasted overnight and pre-medicated with azaperone (Stresnil, Janssen Pharmaceutica, Beerse, Belgium, 4.0 mg/kg i.m.) before transport and further handling. Prior to surgery, the pigs were anaesthetised with 2-bromo-2-chloro-1,1,1-trifluoroethane (Fluothane, Astra Lakemedel, Sodertalje, Sweden), mixed with air and O_2 as a carrier gas, at approximately 0.5–1 l/min in a close-circuit respiratory system (Komesaroff Medical Developments, Melbourne, Australia). In all pigs the left external jugular vein was catheterised using silicon tubing (Silastic, Down Corning Corp., Midland, TX, USA) with an outer diameter of 1.64 mm and an inner diameter of 0.75 mm.

The catheter was exteriorised percutaneously on the dorsal side of the neck (Rengman et al., 2009).

In the first study, eight pigs underwent 5/6 nephrectomy by making use of live tissue welding – biofeedback-based impulse electric coagulation (Podpryatov et al., 2007; Bogdan et al., 2009). A special clamp, connected to a High-Frequency Welding Electrocoagulator EKVZ-300 PATONMED® (Paton Welding Institute, Kiev, Ukraine) was used. The one kidney (in most cases, the left kidney) was removed and the obstruction of blood flow to 2/3 of the remnant kidney was achieved by welding of 2 of the 3 end branches of the renal artery. The pigs were then given 3 weeks for recovery and the development of CKD and hyperuricemia.

In the second study, two pigs underwent 9/10 nephrectomy by ligation of the renal artery of one kidney and obstruction of the blood flow to 4 of the 5 renal artery branches at the second branching of the remnant kidney. These pigs were given 1 week for recovery before the experiments commenced.

Experimental design

The study was composed of three separate experiments. The first experiment was performed using 4 healthy control pigs and 8 nephrectomized (5/6 nephrectomy) pigs. Pigs were fed feed (Wytwórnia Pasz 'Morawski', Kcynia, Poland) enriched with 20% fructose for a period of 3 weeks. Additionally, during the last week of the 3-week period, the pig feed was supplemented with oil (8%) and cream (16%), since a high-fat diet and obesity can also lead to the development of hyperuricemia (Lee et al., 2006). Blood samples were collected at baseline (before surgery) and then on the 13th and 25th day following surgery and plasma UA and creatinine concentrations were assessed. Additionally, other biochemical parameters (urea, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH), alkaline phosphatase (AlkP), γ-glutamyltransferase (GGT), etc.) were analysed in plasma from day 25 following surgery. At the end of the experiment (25th day after surgery) two consecutive 24 h urine sample collections were performed.

The second experiment was performed using 4 healthy pigs maintained on the same diet as that used in the first experiment. The pigs were administered a uricase inhibitor in the form of a potassium oxonate (POx) solution (28 mg/ml of 0.9% sodium chloride, pH 7.4) at 300 mg per kg body weight (b.w.), intravenously through a jugular vein catheter (Fridovich, 1965). The administration was performed in one or two doses (with a 6 h interval between the two doses). Baseline blood samples were taken from the jugular vein catheter before POx administration (time 0 h), and thereafter repeatedly during the day at 2, 4, 8, 12, 18 and 24 h following POx administration. Two consecutive 12 h urine sample collections were performed following POx administration.

The third, preliminary, experiment was performed using only one healthy and two nephrectomized (9/10 nephrectomy) pigs. Nephrectomized pigs were administered POx solution at 300 mg per kg b.w., intravenously through a jugular vein catheter in one infusion. The healthy pig was administered POx solution at 600 mg per kg b.w., also *via* the jugular vein catheter, in two infusions with a 30-min interval between each infusion. Baseline blood samples were taken from the jugular vein catheter before POx administration (time 0 h), and thereafter repeatedly during the day at 10, 20 and 30 min and then 1, 2, 3, 4, 6, 8, 12 and 24 h following POx administration. Urine samples were collected five times during the 9 h following the POx administration.

Blood collection and analyses

Blood samples were collected into lithium-heparin tubes (BD Vacutiner®, Becton, Dickinson and Company, Roborough, UK), that were gently inverted several times after collection and stored on ice before being centrifuged at 3000 *g* for 15 min at 4 °C. Plasma was collected and the samples were stored at −20 °C until further analysis. Frozen plasma aliquots were thawed only once and then used for plasma UA and creatinine concentration determinations. Plasma UA and creatinine concentrations were analysed using commercial kits for UA and creatinine (Cat. No. DIUA-250 and DICT-500, respectively; BioAssay Systems, Hayward, CA, USA), respectively, according to manufacturer's instructions. Other plasma biochemical parameters were analysed at Aleris Medilab (Täby, Sweden).

Urine analyses

To prevent precipitation of salts of UA, 1–2 ml of NaOH (8 M) was added to the containers used for urine collection. After each collection period, aliquots of urine samples were transferred into tubes and stored at –20 °C until further analysis of urine creatinine concentrations. Urine UA concentration was assayed in fresh urine samples. Before measurements, urine samples were diluted 1/10 with distilled H_2O for UA and 1/20 with 7 mM NaOH for creatinine analysis. Urine UA and creatinine concentrations were analysed using commercial kits for UA and creatinine (Cat. No. DIUA-250 and DICT-500, respectively; BioAssay Systems, Hayward, CA, USA) according to manufacturer's instructions.

Statistical analyses

All analyses were carried out using Prism, version 5 (GraphPad Software, Inc, San Diego, CA, USA). Data are presented as mean ± standard deviation (SD). Unpaired, two-tailed, Student's t-test or one-way ANOVA, followed by a Dunnett's post-hoc test, were used to calculate statistically significant differences. $P < 0.05$ was considered statistically significant.

Results

Plasma and urine biochemical parameters in pigs that underwent 5/6 nephrectomy

The surgical procedure and postoperative management did not seem to disturb the overall health status and growth of the operated pigs, except for a period of 5–6 days immediately after surgery, when no weight gain was observed. Both operated and non-operated groups of pigs demonstrated similar body weight gain during the 3-week experimental period, with an average body weight of 28 ± 2.5 kg for both groups at the end of the experimental period.

The basal (before surgery) plasma UA concentration of pigs was 0.53 ± 0.08 mg/dl (Figure 1A). The nephrectomy surgery did not affect plasma concentration of UA in pigs (Figure 1A). At the same time, urinary UA excretion was enhanced by 83% in nephrectomized pigs on day 25 following surgery in comparison to that observed in the control group of pigs (Figure 1B). The fractional excretion of UA (FEUA) in nephrectomized pigs was higher than that in healthy animals on day 25 after surgery (9.15 ± 6.33 vs 2.60 ± 1.10%, respectively).

The plasma creatinine concentration in control pigs was close to 1 mg/dl during the experimental period. In contrast, the nephrectomized pigs displayed significantly increased (by 90%) plasma creatinine concentrations on days 13 and 25 following surgery as compared to healthy pigs (Figure 2A). The amount of creatinine excreted in the urine was virtually the same in both healthy and nephrectomized pigs on day 25 after surgery (Figure 2B). At the same time, creatinine clearance was decreased in nephrectomized pigs as compared to healthy animals on day 25 after surgery (202 ± 85 vs 97 ± 28 ml/min, respectively).

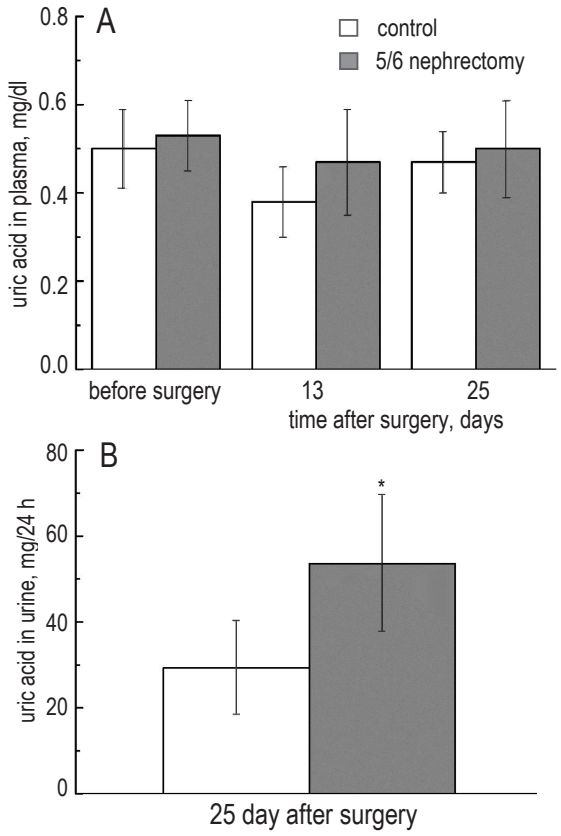

Figure 1. Plasma uric acid concentrations in control (healthy) and nephrectomized (5/6 nephrectomy) pigs before surgery and on days 13 and 25 after surgery (A) and the daily amount of uric acid excreted in the urine on day 25 after surgery (B) (Experiment 1)
data are presented as means ± SD; n = 4 for control group, n = 8 for nephrectomized group; * – indicates significant difference from the control group at $P < 0.05$

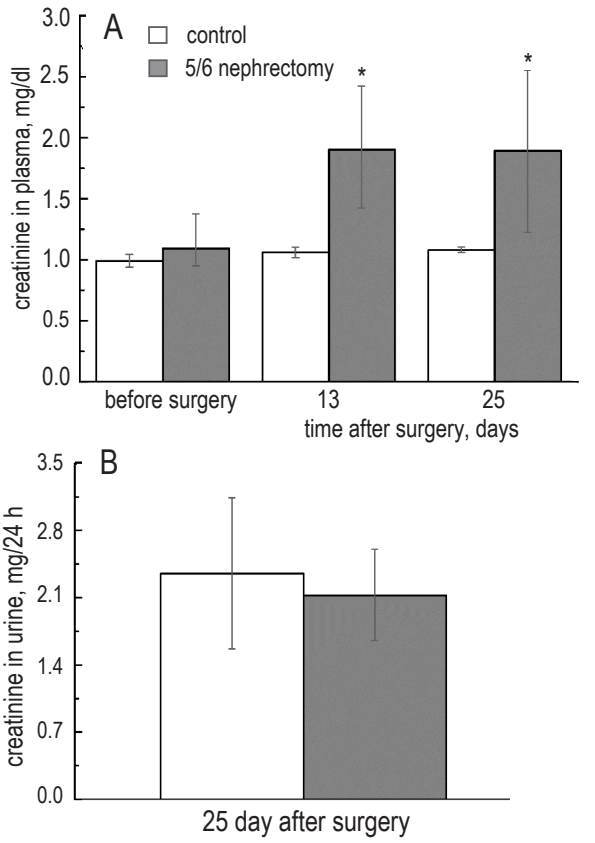

Figure 2. Plasma creatinine concentrations in control (healthy) and nephrectomized (5/6 nephrectomy) pigs before surgery and on days 13 and 25 after surgery (A) and the daily amount of creatinine excreted in the urine on day 25 after surgery (B) (Experiment 1)
data are presented as means ± SD; n = 4 for control group, n = 8 for nephrectomized group; * – indicates significant difference from the control group at $P < 0.05$

Table 1. Plasma biochemical parameters in control and 5/6 nephrectomized pigs on day 25 after surgery (Experiment 1)

Biochemical parameters	Control pigs	5/6 nephrectomized pigs	SD	*P*-value
Urea, mmol/l	1.33	4.33*	2.48	0.011
ALAT, µkat/l	0.74	0.71	0.16	0.658
ASAT, µkat/l	0.33	0.49*	0.14	0.020
LDH, µkat/l	7.94	8.46	1.39	0.547
AlkP, µkat/l	3.26	4.36*	0.91	0.029
GGT, µkat/l	0.45	0.46	0.14	0.746
Cholesterol, mmol/l	3.16	2.80	0.44	0.111
Glucose, mmol/l	6.41	6.18	0.88	0.591
Triacylglycerol, mmol/l	0.31	0.48*	0.13	0.020
AlbP, g/l	14.3	13.2	1.30	0.130
Fe, µmol/l	13.1	27.2	15.8	0.056
P, mmol/l	2.75	2.29*	0.31	0.005
Ca-C, mmol/l	2.65	2.60	0.14	0.397
Na-C, mmol/l	142	142	4.00	0.953
K-C, mmol/l	4.76	4.76	0.25	0.983

AlbP – albumin; ALAT – alanine aminotransferase; AlkP – alkaline phosphatase; ASAT – aspartate aminotransferase; GGT – γ-glutamyltransferase; LDH – lactate dehydrogenase; data are presented as means ± SD; n = 4 for control group, n = 8 for 5/6 nephrectomized pigs; * – indicates significant difference from the control group at $P < 0.05$

Plasma urea concentrations on day 25 after surgery were 3.3-fold higher in nephrectomized pigs than in healthy pigs (Table 1). Activities of ASAT and AlkP were significantly increased (by 48 and 34%, respectively) in nephrectomised pigs in comparison to that observed in healthy pigs. Plasma triglyceride concentrations were 1.5-fold higher in nephrectomized pigs in comparison to the healthy pigs. In contrast, the plasma concentration of phosphate was 1.2-fold lower in nephrectomized pigs, in comparison to that observed in the healthy pigs, but it was in the range of normal values for pigs (2–3.7 mmol/l). The other plasma biochemical parameters that were assessed were not significantly different between the healthy and nephrectomized pigs (Table 1).

Gross examination upon euthanasia of the pigs showed that the kidneys of the healthy control pigs had normal anatomy and structure. The remnant kidneys of pigs that underwent 5/6 nephrectomy surgery had signs of hypertrophy and an irregular shape. The residual functional part has clear lobular form and membrane-like borders, which divides infarct regions (Figure 3). Enlarged kidney size and cortex thickness in pigs with one kidney could probably indicate a compensatory mechanism.

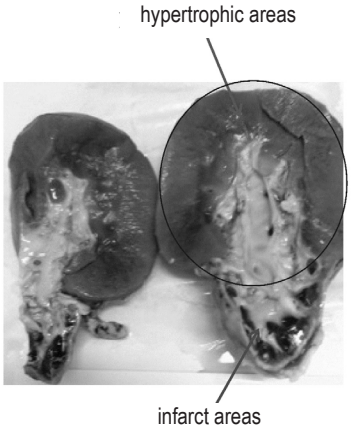

Figure 3. Representative photos of a kidney from a pig subjected to 5/6 nephrectomy surgery, on day 25 after surgery (Experiment 1)

Effect of potassium oxonate on UA turnover in healthy pigs

As shown in Figure 4, the single intravenous infusion of POx (300 mg/kg b.w.) resulted in a 1.5-fold increase in plasma UA concentrations during the 18 h following the POx infusion.

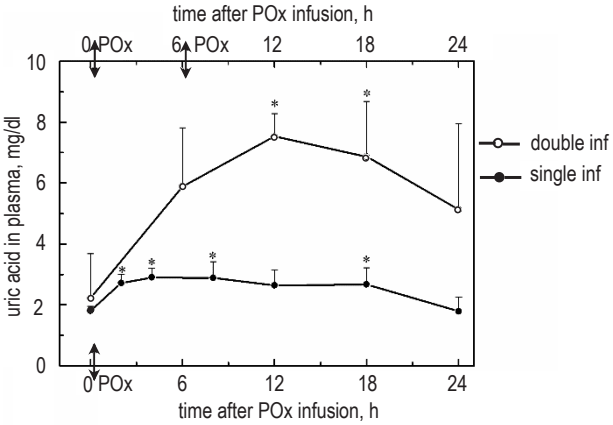

Figure 4. Plasma uric acid concentrations in healthy pigs following a single or double potassium oxonate (POx) infusions (with a 6-h interval between infusions) (Experiment 2)

Potassium oxonate solution (28 mg/ml) was intravenously infused at a dose of 300 mg/kg body weight per infusion; data are presented as means ± SD; n = 4; * – indicates the significant difference from the value before POx injection (separately for single and double infusion group) at $P < 0.05$

At 24 h following POx infusion the plasma UA concentrations returned to baseline (1.80 mg/dl) levels. Urinary UA excretion was significantly increased during the first 12 h after the POx infusion, but returned to baseline levels during the next 12 h (Table 2).

A more pronounced effect of POx administration on plasma UA concentrations was observed after twice-daily infusions with a 6-h interval between

Table 2. Urinary uric acid concentrations (mg/12 h) in healthy pigs after a single or double administration of potassium oxonate (POx) (Experiment 2)

	Uric acid excretion in urine, mg/12 h		SD
	0–12 h	12–24 h	
Baseline, mg/12 h	64.7 ± 18.6		
POx solution infusion (1×)	140	57.4	27.8
POx solution infusion (2×)	914	831	307

data are presented as means ± SD; n = 4

infusions. As shown in Figure 4, plasma UA concentrations significantly increased by 2.5–3.5-fold compared to baseline levels (2.2 mg/dl) during the 18 h after the first POx infusion. The amount of UA excreted in the urine increased significantly over the 24 h following the first POx infusion (Table 2).

Effect of POx on plasma UA concentrations in pigs that underwent 9/10 nephrectomy

Figure 5 shows plasma UA concentrations of one healthy control pig and two nephrectomized pigs (9/10 nephrectomy) after infusion (i.v.) of POx. In all three pigs the plasma UA concentrations remained elevated during the 24 h following infusion of POx and reached a maximum level following 24 h.

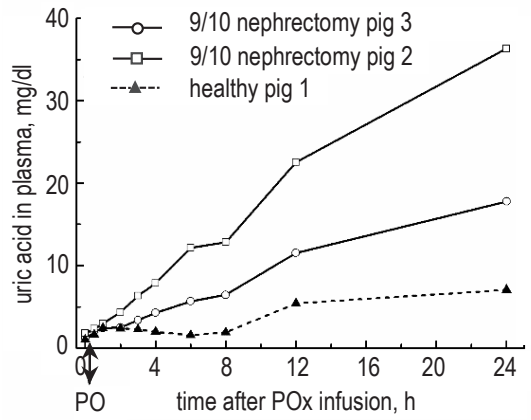

Figure 5. Plasma uric acid concentrations of one healthy and two 9/10 nephrectomized pigs following administration of potassium oxonate (Experiment 3)

Potassium oxonate solution (28 mg/ml) was singly intravenously (i.v.) infused at a dose of 300 mg/kg body weight (b.w.) to the 9/10 nephrectomized pigs. The healthy pig was i.v. infused at a dose of 600 mg/kg b.w. of potassium oxonate, in two infusions with a 30-min interval between infusions. The data represents the results from one representative experiment.

In the two nephrectomized (9/10 nephrectomy) pigs, the plasma UA concentrations were 13- and 20-fold higher than baseline (1.5 mg/dl) 24 h after administration of 300 mg/kg b.w. of POx. At the same time, the healthy control pig demonstrated only a 7-fold increase in plasma UA concentration 24 h after administration of 600 mg/kg BW of POx.

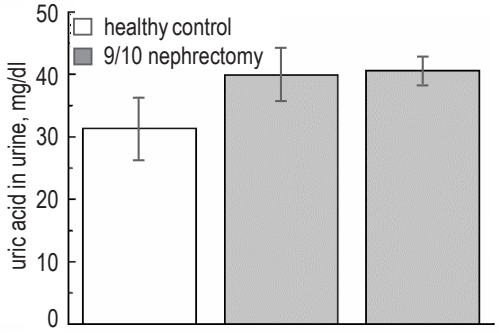

Figure 6. Urinary uric acid concentrations of one healthy and two 9/10 nephrectomized pigs during the 9 h following the potassium oxonate infusion (intravenous) (Experiment 3)

data are the mean of 5 urine sample collections

Urinary UA concentration was elevated in nephrectomized (9/10 nephrectomy) pigs compared to that observed in the healthy control served in the healthy control pig during the 9 h following POx infusion (Figure 6).

Discussion

Concentrations of UA might have a great impact on the monitoring, diagnosis, prognosis and therapy of several renal disorders (Fathallah-Shaykh and Cramer, 2014). Uric acid levels in most mammals are lower than in humans due to the presence of hepatic enzyme uricase, which degrades UA to allantoin (Mandal and Mount, 2015). Therefore, manipulations with UA level in animals are of great interest and can lead to maintain appropriate models for the preclinical *in vivo* evaluation of potential drugs for hyperuricemia in human.

Numerous studies suggest that the development of CKD is associated with the increased serum UA level (Kang and Nakagawa, 2005; Gupta et al., 2011; de Oliveira and Burini, 2012; Johnson et al., 2013a). CKD is a common disease worldwide, characterized by irreversible, progressive and slow loss of the renal function, which affects diverse systems of the organism. In developed countries, CKD is generally associated with old age, diabetes, hypertension, obesity and cardiovascular diseases (Levey and Coresh, 2012; Jalal et al., 2013). Animal models of CKD approximate the human condition and are keys to understand its pathogenesis and to develop rational treatment strategies. There is a lot of protocols in the literature describing development of different animal models of CKD. The most common technique used is the 5/6 reduction of renal mass, either by surgical resection or by infarction (Heyman et al., 2011). In our first experiment we performed 5/6 nephrectomy surgery in juvenile

pigs and examined the plasma and urinary UA and creatinine concentrations during the three weeks after surgery. The restriction of kidney function by 75–90% had no impact on plasma UA concentrations in pigs, most probably due to increased activity of the liver enzyme, uricase. At the same time, plasma creatinine concentrations were elevated in the 5/6 nephrectomized pigs, indicating failure of kidney function. Similar results were observed by Hatch and Vaziri (1994) in rats with chronic renal failure. Moreover, these authors showed alterations in intestinal urate transport in rats with chronic renal failure in comparison to that of normal rats. In our previous study we also demonstrated that UA, after reaching a certain plasma urate threshold, can be eliminated *via* the intestine in pigs (Szczurek et al., 2017). In addition, Simmonds et al. (1976) suggested that porcine kidneys handle urate as an organic acid, which can thus be eliminated very effectively by filtration and secretion.

We also evaluated several other plasma biochemical parameters related to kidney function, in particularly urea which concentrations were significantly higher in the 5/6 nephrectomized juvenile pigs than in healthy pigs. Our results are similar to those observed by Gupta et al. (2011) and indicate the decreased ability of the kidney to clear urea from the bloodstream in the 5/6 nephrectomized pigs. The significantly increased plasma triglyceride concentrations observed in the 5/6 nephrectomized pigs could indicate the development of metabolic disorders related to the high-fat diet or kidney failure (Vaziri, 2006). Additionally, upon autopsy of the 5/6 nephrectomized pigs, hypertrophic re-growth of the 1/6 part of the kidney was observed, which could assist kidney filtration.

It was reported that fructose can induce renal hypertrophy and tubulointerstitial disease, as well as increase serum uric acid level due to ATP depletion and increased purine destruction (Kretowicz et al., 2011; Johnson et al., 2013b). However, experimental data in the literature is contradictory. For example, Gersch et al. (2007) showed that administration of fructose to rats with reduced renal function (the remnant kidney model) can accelerate the progression of renal disease, resulting in worse proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis. Other authors reported no effect of low-fructose diet for a period of 6 weeks on renal function of humans with stable chronic kidney disease (Kretowicz et al., 2011). As mentioned, fructose can increase intracellular and circulating UA levels due to increased nucleotide turnover and synthesis, as well as due to stimulation UA synthesis from amino acid precursors, such as glycine (Johnson et al., 2013b). It was suggested, that rodents show a lesser rise in serum UA in response to fructose due to the presence of uricase in their liver and hence lower serum UA than humans (Stavric et al., 1976). In our study, the consumption of the high-fat diet enriched with 20% of fructose for 3 weeks did not result in the rise of plasma UA, in both healthy and nephrectomized pigs, that is in contrast to results reported in previous studies (Kretowicz et al., 2011; Johnson et al., 2013b).

It is known, that in laboratory animals it is possible to modulate the UA level by using a uricase inhibitor such as oxonic acid, as well as with xanthine oxidase inhibitors or uricosuric agents (Stavric and Nera, 1978; Murota et al., 2012; Johnson et al., 2013a). Therefore, in the follow-up experiments we made use of the uricase inhibitor, potassium oxonate. Fridovich (1965) found that the potassium salt of oxonic acid, an oxidative derivative of UA, was the most potent competitive inhibitor of uricase *in vitro*. Later, Stavric et al. (1969) showed that inhibition of uricase by POx in experimental animals might lead to a long lasting hyperuricemic condition that could be used as a model of the human disease. Since then, the aforementioned model was used in many studies to induce hyperuricemia in animals (Stavric et al., 1976; Yonetani et al., 1980; Murota et al., 2012; Hu et al., 2013). In our experiments, i.v. infusion of POx to healthy pigs resulted in a significant increase in plasma UA concentrations, with the plasma UA concentration remaining at a relatively stable level during the 18 h following POx administration. The 9/10 nephrectomized pigs demonstrated a significant increase in plasma UA concentrations for more than 24 h after a single infusion of POx. Simultaneously, urinary UA concentrations were significantly increased in POx treated pigs, indicating enhanced excretion of UA. The latter results agree with those reported earlier, where oxonic acid led to increased urinary UA excretion in pigs from 5 mg to 900 mg per 24 h (Hatfield et al., 1974). Previously, Yonetani et al. (1980) showed that administration of POx (i.p.) every 2 h resulted in a prolonged high concentration of UA in the plasma of rats.

Conclusions

The present study expands today available data on uric acid metabolism in juvenile pigs and justified the usage of pigs as model for uric acid metabolism in human. The 5/6 nephrectomized pigs could

be used as a model for the study of diseases related to kidney failure while rather not for uric acid metabolism, while the 9/10 nephrectomized pigs could be used as a model to study hyperuricemia and hyperuricemia-associated kidney failure.

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