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ORIGINAL PAPER

Exhaustive exercise decreases renal organic anion transporter 3 function

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Abstract

This study aimed to investigate the effects of various types of exercise on organic anion transporter 3 (Oat3) function, a major transporter that plays a role in the secretion of a variety of drugs and endogenous compounds. Male Wistar rats were randomly allocated to non-exercise, exhaustive, acute and training exercise groups. The function of Oat3 was assessed by the uptake of [^{3}H]-estrone sulfate ([^{3}H]-ES) into rat renal cortical slices. Acute and training exercises had no effect on [^{3}H]-ES uptake whereas a marked reduction in [^{3}H]-ES uptake occurred immediately after exhaustive exercise. However, the reduction in Oat3 function was gradually recovered at 6 and 24 h after the exercise session. Importantly, the impairment of Oat3 function was associated with a decrease in renal Oat3 protein expression. Our results indicate that exhaustive exercise produces a significant impact on renal organic anion transport function, which in turn could alter the plasma level of drugs and compounds in the body.

Keywords Exercise · Exhaustive exercise · Training · Renal secretory process · Organic anion transporter 3

Introduction

It is well recognized that exercise is good for our health and well-being. Regular exercises have been prescribed as medicine for treatment and prevention of chronic diseases worldwide [1]. Indeed, exercise has been recommended in combination with drug therapy to improve patients' health conditions and quality of life. Several lines of evidence show that exercise induces several physiological changes and adaptations. Acute exercise increases blood flow to cardiac and active skeletal muscles, whereas blood flows to inactive skeletal muscles, splanchnic, and kidneys are reduced in order to match the energy demand during exercise [2, 3]. At rest, blood flow to kidneys is approximately 22% of cardiac output. During exercise, an amount of blood is shunted from kidneys toward working muscles in proportion to exercise intensity. Thus, blood flow to kidneys decreases markedly to 10, 3 and 1% of cardiac output during low, moderate, and high intensity exercise, respectively [2]. The reduction in blood flow to kidneys during exercise could affect renal function and its tubular transport processes, which in turn may alter drug pharmacokinetics and plasma level of various compounds [4–6].

The kidney is a primary organ that is responsible for drug clearance from the body. Disruption of the kidney and its secretory functions during exercise could alter the plasma level of various drugs and endogenous compounds. Accumulating evidence showed that exercise suppressed renal clearance of tetracycline, doxycycline, sulphamethizole and sulphadimidine with corresponding increases in plasma concentrations of these drugs [7, 8]. Since the renal secretory process plays a pivotal role in elimination of various compounds, an alteration in the renal secretory process would have a significant impact on their plasma concentrations [5, 9]. At present, there is nearly no information concerning the effect of various types of exercise on renal tubular function, especially secretory processes.

Organic anion transporters (Oats), expressed in the renal proximal tubule, have a significant role in the tubular

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secretion of various compounds including drugs, endogenous substances, and toxic compounds [10]. Oats, located at the basolateral membrane of renal epithelial cells, mediate secretion via uptake of organic anions from blood into cells across the basolateral membrane, and subsequently secrete into the tubular lumen [11]. At present, several members of Oats have been cloned and identified, including Oat1, 2, 3 and 4 [10]. Among these, Oat3 has the highest expression level in human and rat kidneys and is considered to play a major role in secretion of clinically important drugs from blood to urine, including anti-viral therapeutics, anti-cancer drugs, antibiotics, anti-hypertensive, and anti-inflammatory drugs [12–14]. Therefore, an impairment of Oat3 function would result in a decreased renal tubular secretion and an increased serum concentration of therapeutic drugs and endogenous compounds [15, 16]. As mentioned earlier, exercise induces renal hemodynamic changes and has potential to alter renal function as well as its elimination of various drugs and compounds. However, information concerning the impact of various types of exercise on renal secretory function is still lacking. In the present study, we investigated the effects of various types of exercise including acute exercise, exhaustive exercise, and exercise training on Oat3 transport function. The results obtained from our study provide novel information concerning the impact of exercise on renal secretory process. This could be very helpful for the healthcare profession in taking care of exercising persons who may be at a particularly high risk of drug accumulation.

Methods

Animals

Male Wistar rats were obtained from the National Laboratory Animal Center (Nakhon Pathom, Thailand) and housed in an environmentally controlled room at the Laboratory Animal Facility, Faculty of Science, Mahidol University, according to the standards of the Guidelines of the National Laboratory Animal Center of Thailand. Rats were fed with standard rat chow and water ad libitum and maintained at 25 ± 2 °C with a 12-h dark–light cycle. All animal procedures were approved by the Animal Care and Use Committee of the Faculty of Science, Mahidol University, Thailand (MUSC57-006-298).

Study design

This study was designed as an age-matched control study. After a 1-week acclimatization, male Wistar rats (age 6 weeks, weight 200–250 g) were randomly divided into 4 groups according to the types of exercise and protocols indicated below. Group 1, the non-exercise group (NE), was used as the non-exercise control group. In group 2, the exhaustive exercise group (EE), rats performed exercise until exhaustion. In group 3, the acute exercise group (AE), rats performed a single bout of exercise for 60 min. In group 4, the exercise training group (TE), rats were subjected to exercise for 60 min, 5 times/week for 8 weeks.

Exercise protocols

Exhaustive exercise. On the day of experiment, rats began to run on a motorized treadmill at a speed of 16 m/min with 0° inclination, then the speed was gradually adjusted to 24 m/min with 15° inclination within 5 min. This running speed was maintained for 10 min. After that, the running speed was gradually increased to 38 m/min until exhaustion. The sign of exhaustion was determined by the loss of ability to rise up on the four legs [17]. The rats were sacrificed by sodium pentobarbital (100 mg/kg BW, intraperitoneal injection) at various time points (immediately, 6 and 24 h) after exhaustive exercise, and the kidneys were removed for the determination of Oat3 function.

Acute exercise. On the day of the experiment, rats were subjected to running on a motorized treadmill for 60 min at a speed of 20 m/min with a 15° inclination. Immediately after exercise, the rats were sacrificed and the kidneys were removed for subsequent studies.

Training exercise. Rats were introduced to a motorized treadmill so as to be familiar with treadmill running for 5 days. During the first 2 days, rats ran on the treadmill at a lowest speed (16 m/min, 0° inclination) for 10 min. For the following 3 days, rats ran at 18 m/min, 0° inclination for 20 min. Then, the running speed, inclination, and duration were gradually increased to 20 m/min, 15° inclination for 60 min/day, 5 days/week. Rats performed exercise training for 8 weeks. To avoid the effect of acute exercise, they were allowed to rest for 24 h after the last exercise session, prior to sacrifice for subsequent studies.

Renal slice preparation and uptake study

The function of Oat3 was determined by the uptake of [^{3}H]-estrone sulfate ([^{3}H]-ES) [18, 19]. At the end of the exercise session, rats were sacrificed by sodium pentobarbital (100 mg/kg BW, intraperitoneal injection). Kidneys were removed, decapsulated and kept in ice-cold modified Cross and Taggart buffer (95 mM NaCl, 80 mM mannitol, 5 mM KCl, 0.74 mM $CaCl_2$, and 9.5 mM Na_2HPO_4, pH 7.4). The renal cortical slices (≤ 0.5 mm, 5–10 mg/slice) were cut using a Stadie-Rigge microtome and incubated for the uptake study in an ice-cold buffer for 10 min. Then, slices were incubated in buffer containing 30 nM of [^{3}H]-ES (Perkin Elmer Waltham, MA, USA) at 37 °C for 30 min. The uptake of [^{3}H]-ES was stopped by washing the renal slices

3 times with an ice-cold buffer containing 1 mM unlabeled-ES. Wet slices were then blotted, weighed and dissolved in 1 N NaOH for 24 h and neutralized with 1 N HCl. Tissue samples were determined for [^{3}H]-ES using a Liquid Scintillation Analyzer (1214 Rackbeta, Wallac). The uptake was calculated as tissue per medium ratio (T/M) (dpm/mg of tissue ÷ dpm/µl uptake buffer) and expressed as a percentage of control.

Western blot analysis

The rat renal cortex was dissected and homogenized using a Polytron PT3100 homogenizer (Kinematica AG, Lucerne, Switzerland) in an ice-cold homogenization buffer (300 mM sucrose, 25 mM imidazole, 1 mM EDTA, 1 mM PMSF, and complete protease inhibitor, pH 7.2). A complete protease inhibitor was obtained from Roche Diagnostics, Germany, and used for the inhibition of serine and cysteine proteases in the tissue extracts. Tissue homogenate was centrifuged at 12,000 rpm for 20 min at 4 °C and the supernatant was collected and kept at − 80 °C for subsequent analysis. The protein of the supernatant was separated by 10% SDS-PAGE and transferred to a nitrocellulose membrane (Millipore, Billerica, MA, USA). The membranes were blocked with 5% non-fat dry milk in TBST (Tris-buffered saline, 0.1% Tween 20) at room temperature for 1 h. The membranes were then incubated overnight with polyclonal rabbit anti-Oat3 antibody (Cosmobio, Tokyo, Japan; no. KAL-KE035; 1:500 dilutions). After washing with TBST, the membranes were probed with horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG (Cell Signaling Technology, USA, 1:3000 dilutions) at room temperature for 1 h. The immunoreactivity was developed using an enhanced chemiluminescence (ECL) detection kit. The protein expression signals were quantified using Image J software (NIH, Bethesda, MD, USA).

Biochemical analysis

On the day of the experiment, blood was collected using a cardiac puncture technique under anesthesia. The serum was separated by centrifugation at 3000 rpm at 4 °C for 10 min. These samples were analyzed for serum blood urea nitrogen (BUN) and serum creatinine as indicators of renal function. They were analyzed by enzymatic colorimetric techniques using commercial kits (Biotech, Bangkok, Thailand).

Statistical analysis

All data were expressed as mean ± SEM. For multiple comparisons, data were analyzed with one-way ANOVA followed by Bonferroni post hoc test. Data analysis was performed using GraphPad Prism software. The level of significant difference was set at p values < 0.05.

Results

Effects of different types of exercise on general characteristics

The general characteristics of non-exercise (control), exhaustive, acute, and training exercise rats were determined. As shown in Table 1, all experimental rats were age-matched with controls (15 weeks old). Acute and exhaustive exercise had no effect on rat body weight when compared with non-exercise rats. On the other hand, training exercise produced a 7% reduction in rat body weight compared to that of non-exercise rats ($p < 0.05$). However, all exercise groups had no change in kidney weight. As a result, kidney/body weight ratio significantly increased in trained rats compared to that of non-exercise rats ($p < 0.001$). The significant increase in kidney/body weight ratio in trained rats was likely due to the decrease in body weight from adaptation to exercise training.

Effects of different types of exercise on renal parameters

The elimination of compounds from the kidney involves glomerular filtration and tubular secretion. To assess the effect of exercise on renal function, serum creatinine and BUN were used as indicators to estimate the glomerular filtration rate (GFR) in all experimental groups [20, 21]. As shown in Table 2, only the exhaustive exercise group seemed to have a slightly higher serum creatinine level than that of other groups, but it did not reach statistical significance. There were no significant differences in BUN

Table 1 General characteristic of experimental rats

	Age (weeks)	Body weight (g)	Kidney weight (g)	Kidney/body weight ratio
Non-exercise (NE)	15	502.02 ± 12.71	1.31 ± 0.03	0.26 ± 0.01
Exhaustive exercise (EE)	15	496.47 ± 13.62	1.35 ± 0.03	0.27 ± 0.01
Acute exercise (AE)	15	512.93 ± 11.04	1.37 ± 0.02	0.27 ± 0.01
Training exercise (TE)	15	467.01 ± 6.54*	1.37 ± 0.04	0.30 ± 0.01***

Values are means ± SEM (n = 7–12 rats per group). *$P < 0.05$, ***$P < 0.001$ versus non-exercise group

Table 2 Effect of different types of exercise on renal function parameters

	Serum creatinine (mg/dl)	BUN (mg/dl)
Non-exercise (NE)	0.29 ± 0.06	37.58 ± 1.47
Exhaustive exercise (EE)	0.38 ± 0.06	38.72 ± 1.83
Acute exercise (AE)	0.24 ± 0.06	40.95 ± 2.47
Training exercise (TE)	0.25 ± 0.05	36.67 ± 1.39

Values are means ± SEM ($n = 7$–9 rats per group)

BUN blood urea nitrogen

among experimental groups. The results suggest that none of the exercise regimes in this study had a significant effect on GFR.

Effects of different types of exercise on Oat3 function

The function of Oat3 was assessed by the [^{3}H]-ES uptake into rat renal cortical slices. As shown in Fig. 1, there were no significant differences in [^{3}H]-ES uptake into rat renal cortical slices among non-exercise, acute exercise, and training exercise groups. Nevertheless, a significant decrease in [^{3}H]-ES uptake into rat renal cortical slices was observed immediately after exhaustive exercise compared to that of the non-exercise group ($p < 0.05$). These results indicate that exhaustive exercise decreased Oat3 transport function immediately after exercise.

Recovery of Oat3 transport function after exhaustive exercise

As described above, immediately after exhaustive exercise, [^{3}H]-ES uptake into rat renal cortical slices significantly decreased by about 35% compared to that of non-exercised rats ($p < 0.05$) (Fig. 2). However, the [^{3}H]-ES uptake was gradually restored at 6 h (28% reduction) and 24 h (17% reduction) after exhaustive exercise, respectively. These results indicate that the decrease in Oat3 transport function after exhaustive exercise occurred only temporarily and could be reversed at 6 h after exhaustive exercise.

Effect of exercise on Oat3 protein expression

The function of Oat3 depends largely on the amount of Oat3 protein expression. Therefore, the expression level of Oat3 protein after exercise was determined. As indicated in Fig. 3b, in accordance with the transport function, the relative protein expression of Oat3 was significantly decreased immediately after exhaustive exercise compared to that of non-exercise ($p < 0.05$). Of note, Oat3 protein expressions among non-exercise, acute, and training exercise groups were not different. Interestingly, we found the recovery of Oat3 transport function was associated with an increased Oat3 protein expression level during the recovery period after exhaustive exercise. The relative protein expression level of Oat3 was gradually increased at 6 h and 24 h after exhaustive exercise compared to that of the non-exercise group (Fig. 4b). These findings clearly indicate that the reduction in Oat3 protein expression level after exhaustive exercise accounts for the decrease in Oat3 transport function.

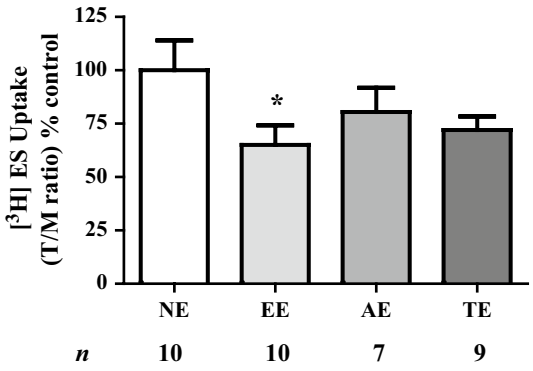

Fig. 1 Effect of different types of exercise on [^{3}H]-ES uptake into rat renal cortical slices. Rat renal cortical slices from non-exercise (*NE*), exhaustive exercise (*EE*) (immediately after exercise), acute exercise (*AE*) and training exercise (*TE*) groups were incubated in uptake medium containing 30 nM [^{3}H]-ES for 30 min. The uptake was calculated as the tissue-to-medium ratio and was expressed as a percentage of the uptake in the non-exercise group. Values are mean ± SEM. *$P < 0.05$ versus non-exercise group. *n* is the number of experimental rats

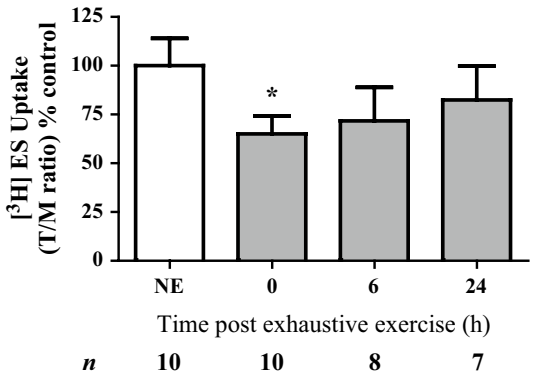

Fig. 2 The recovery of [^{3}H]-ES uptake into rat renal cortical slices after recovery from exhaustive exercise. Immediately (0 h), 6 and 24 h after exhaustive exercise, rat renal cortical slices were obtained and [^{3}H]-ES uptake was determined as described previously. The uptake was calculated as the tissue-to-medium ratio and expressed as a percentage of non-exercise (*NE*) group. Values are mean ± SEM. *$P < 0.05$ versus non-exercise group. *n* is the number of experimental rats

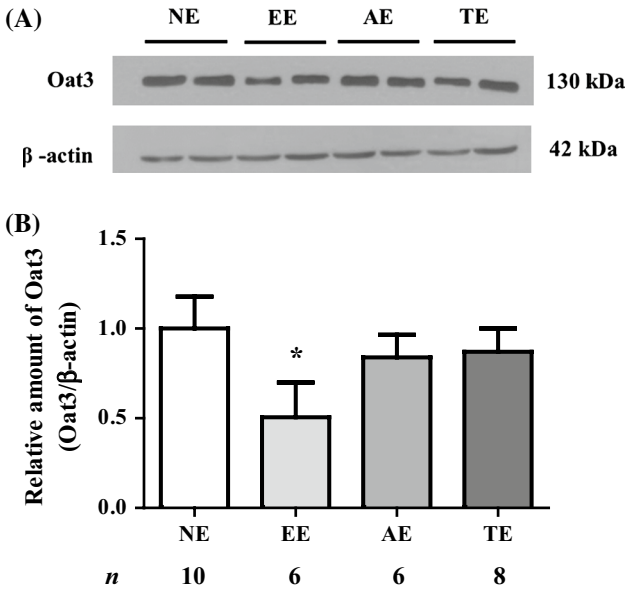

Fig. 3 Effect of different types of exercise on Oat3 protein expression in renal cortex. **A** Representative blots. **B** Densitometric quantification of Oat3 protein expression. At the end of the exercise session, total renal cortex proteins were extracted and examined for Oat3 expression. Oat3 protein expression was normalized by β-actin and expressed as a relative value to the non-exercise group. Values are mean ± SEM. $^*P < 0.05$ versus non-exercise group. *n* is the number of experimental rats

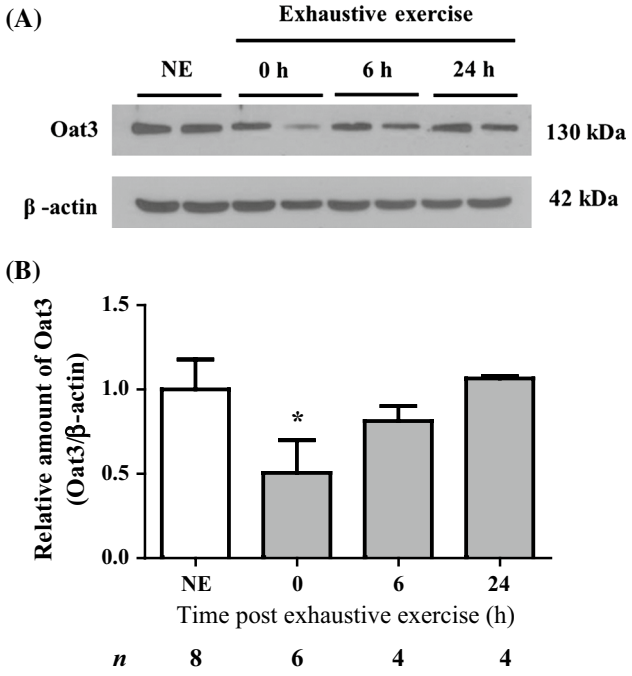

Fig. 4 The reversibility of Oat3 protein expression in renal cortex during recovery from exhaustive exercise. **A** Representative blots. **B** Densitometric quantification of Oat3 protein expression. Immediately (0 h), 6 and 24 h after exhaustive exercise, total renal cortex proteins were extracted and examined for Oat3 expression. Oat3 protein expression was normalized by β-actin and expressed as a relative value to the non-exercise group. Values are mean ± SEM. $^*P < 0.05$ versus non-exercise group. *n* is the number of experimental rats

Discussion

In the present study, we addressed the question of whether exercise had an effect on renal transport function, especially Oat3 function, which is a major protein transporter responsible for renal secretion of a variety of drugs and compounds. The main finding is that immediately after exhaustive exercise, Oat3 transport function in rat renal cortical slices was markedly reduced. The reduction of Oat3 function resulted from a decrease in Oat3 protein expression in the renal cortex. Interestingly, the declines in Oat3 transport function and protein expression were only temporary. Both gradually recovered at 6 and 24 h, respectively, after exhaustive exercise.

To our knowledge, the present study is the first study to investigate the effects of various types of exercise (exhaustive, acute and training exercise) on renal secretory function focused on the major transport protein (Oat3) in the renal proximal tubule. It has long been known that intensity and duration of exercise could alter the renal function [2]. Therefore, the effects of different types of exercise on renal transport function were investigated in this study. The exhaustive exercise in the present study represents unaccustomed high intensity exercise. In this setting, rats performed treadmill running at 38 m/min until exhaustion, and the loss of ability to rise up on their legs was used as an exhaustive index [17].

The acute exercise was a single episode of exercise in which the intensity and duration of exercise were equivalent to moderate exercise intensity. Acute exercise was performed to examine an acute physiological response of renal Oat3 function after a single episode of moderate exercise intensity. Training exercise, on the other hand, consists of repeated episodes of moderate intensity exercise, which induces several physiological parameter adaptations to training, including increased cardiovascular endurance and enhanced metabolic adaptation as well as changes in body weight [2, 22]. We found that after 8 weeks of training, the trained rats had lower body weights than those of the non-exercise rats. This is in agreement with a previous study showing that exercise training increased the metabolic rate or energy expenditure, resulting in a decrease in body weight [23]. Therefore, the reduction in body weight gain after training exercise in the present study is likely to be due to the metabolic adaptation to exercise training.

Immediately after exhaustive exercise, the rats in this group had a slight increase in serum creatinine, but it was not significant compared to the non-exercise group. The increase in serum creatinine could partly be due to induced muscle breakdown as well as decreased tubular secretion

of creatinine via decreased Oat3 function after exhaustive exercise [24–26]. In view of no significant changes in BUN, the elevated serum creatinine after exhaustive exercise was unlikely to be due to an alteration in GFR.

As Oat3 transport activity was decreased immediately after exhaustive exercise, we speculated that it could be due to reduced Oat3 protein expression. Indeed, the amount of Oat3 protein expression decreased significantly after exhaustive exercise. However, the reduction in Oat3 protein expression was recovered at 6 and 24 h after exercise, which is in line with the restoration of Oat3 transport function. Our finding suggests that the reduction in Oat3 protein expression accounted, in part, for the decline in Oat3 transport function immediately after exhaustive exercise. It is well recognized that protein expression is regulated at transcriptional level; we therefore determined whether a decrease in Oat3 protein resulted from a reduction of Oat3 mRNA. A previous study demonstrated that impaired organic anion *p*-aminohippurate (PAH) secretion was accompanied by decreases in Oat1 and Oat3 mRNA and protein expression observed after ischemic acute renal failure [27]. However, we found that the amount of Oat3 mRNA tended to decrease immediately after exhaustive exercise but it did not reach statistical significance compared to non-exercise (data not shown). This finding suggests that the decline in Oat3 transport function in our study may not be due to the decrease in protein synthesis. Alternatively, it could be attributable to increased protein degradation. This notion, however, requires further studies.

As mentioned above, the impairments of Oat1 and Oat3 protein expressions were induced by bilateral clamping of renal arteries for 45 min; it is also possible that the exhaustive exercise in our study may markedly reduce renal blood flow due to intense sympathetic activation similar to the condition of acute renal failure. Unfortunately, the renal blood flow during exhaustive exercise was not measured in our study. Nevertheless, our previous study showed that activation of α1-adrenergic receptor by phenylephrine reduced [^{3}H]-ES uptake into rabbit renal proximal tubule [28]. Of note, the α1-adrenergic receptor could be markedly stimulated by norepinephrine and epinephrine, which were increased during exercise [29]. It has been shown that the levels of norepinephrine and epinephrine during exercise were progressively increased in exercising skeletal muscle, heart, kidney, and liver in an intensity-dependent manner [30–32]. Plasma norepinephrine and epinephrine increased approximately 14 and 8 times, respectively, during high intensity exercise when compared with a resting condition. This would markedly stimulate α1-adrenergic receptor and result in decreased blood flow to the kidneys. Therefore, the reduced Oat3 transport function could be a consequence of increased activity of α1-adrenergic receptors along with markedly decreased renal blood flow during exhaustive exercise. In contrast, renal plasma norepinephrine spillover was reduced after 1-month endurance training, indicating that exercise training reduced whole-body and renal resting sympathetic activity [33]. This report was in line with our finding that training prevented a decrease in Oat3 function. Therefore, exhaustive exercise is likely to increase plasma norepinephrine and epinephrine, which in turn stimulate α1-adrenergic receptors and contribute to reduced Oat3 transport activity and protein expression. In contrast, training produces less increase in plasma norepinephrine and epinephrine, hence preventing the decline of Oat3 function. Unfortunately, however, plasma levels of norepinephrine and epinephrine after exercise were not examined in our study. Previously, we reported that activation of α1-adrenergic receptors inhibited Oat3 transport activity via activation of protein kinase C (PKC) [28]. In addition, a recent study found that PKC regulated Oat3 transport activity and protein expression through Oat3 ubiquitination [34]. Therefore, the reduction in Oat3 transport function and expression after exhaustive exercise may result from an increase in its degradation. However, the exact mechanism by which exhaustive exercise reduced Oat3 activity needs further investigations.

In summary, this is the first report showing that intensity and types of exercise can affect renal secretory function. Importantly, exhaustive exercise decreased Oat3 transport function by downregulating its expression in the kidney. Therefore, healthcare professionals should consider this information when taking care of people who may have a high risk of drug accumulation from participating in heavy exercise regimes.

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Author contributions TB, CY, and RN performed biochemical assays, uptake study, and animal experiment. TB analyzed data, interpreted results and wrote the manuscript. TB and VC designed the project. VC supervised the project and revised the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures in this study were conducted in accordance with the guidelines of the National Laboratory Animal Center of Thailand. The protocol was approved by the Animal Care and Use Committee of the Faculty of Science, Mahidol University, Thailand (MUSC57-003-298).

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