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The Effect of Methylphenidate and Aerobic Exercise on Renal Function of Male Rats

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Abstract

Introduction: Inadequate awareness and knowledge exists regarding the effects of stimulant drugs on renal health among athletes. The present study aimed to determine the effects of methylphenidate, as a stimulant drug, and aerobic exercise on renal function in rats.

Materials and Methods: Eighty male rats were randomly divided into 8 groups (n=10 per group) including control (Co), aerobic exercise sham (AE Sh), drug sham (D Sh), aerobic exercise (AE), the effective dose of drug (ED, 10 mg/kg), 3 times of effective dose (TED, 30 mg/kg), aerobic exercise-effective dose (AE-ED), and aerobic exercise-three times of effective dose (AE-TED). The drug was orally administrated to the animals, and then they were placed on a rat treadmill after 30 minutes. The physical activity (25 m/min) was performed 30 minutes a day, 3 days a week for two months. Twenty-four hours after the last session of AE, blood samples were taken from the rats and serum creatinine (Cr) and blood urea nitrogen (BUN) were determined.

Results: The results showed that serum Cr and BUN levels were not significantly different in the exercise group compared to the control groups (i.e., Co, AE Sham, and D Sham). However, serum BUN and Cr significantly increased in the AE-ED and AE-TED groups compared to the AE group (P_{Cr}=0.001 and P_{BUN}=0.001).

Conclusion: In general, significant increases in the serum BUN and Cr levels in rats received methylphenidate indicated decreased renal function in these animals.

Keywords: Methylphenidate, Aerobic exercise, Rat, Blood urea nitrogen, Creatinine

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Introduction

So far, an increase in the number of doping cases in sports competitions, especially in the Olympic Games has obsessed the sports experts' minds. The word "doping" is derived from the Dutch word "dop" which refers to the skin of the grapes from which Zulu warriors made wine to give them courage in the battles. The term entered the modern lexicon in the 19th century.[1-4] According to the International Olympic Committee (IOC), a positive doping case was announced in the 1968 Olympics in Mexico City and11 cases of doping tests were positive in the Sydney Olympics (2000).[5] In addition, the rising trend of positive tests was reported in the Athens (2004) and Beijing (2008) Olympics.[4] Further, the truth committee of the world anti-doping agency confirmed the organized and sponsored doping in Russia. McLaren reported that Russian athletes doped with the state support during the Sochi Winter Olympics (2014).[6]

According to the IOC reports, the most commonly misused drugs were anabolic steroids (nearly 65%), stimulants (20%), and diuretics (4%).[7] Stimulant drugs were considered the first compounds based on which the death or acute complications were reported due to their consumption.[8] Methylphenidate (MPH) stimulant drug was the case which was studied in this research.[9] Stimulants are known as the sympathomimetic drugs as well.[10] This nerve stimulator has a high potential for

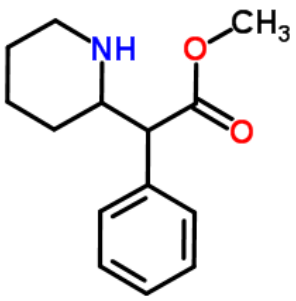

Figure 1. Chemical Structures of Methylphenidate.

abuse, and it has a cocaine and methamphetamine-like structure (Figure 1). Furthermore, its effects are created by inhibiting the reuptake of dopamine and norepinephrine neurotransmitters in the synapse gap.[11,12]

The concentration of MPH in the brain is higher than its blood level[13,14] and ritalinic acid is regarded as the main metabolite of MPH.[15,16] Moreover, MPH can trigger responses such as behavioral sensitivity or high tolerance at 10 mg/kg dose.[17] Sympathomimetic agonists prevent the reuptake of catecholamines (i.e., norepinephrine, epinephrine, and dopamine) by the presynaptic membrane (Figure 2) thus, the synaptic activity of the neurotransmitters prolong the effects of nerve mediators by inhibiting the enzymes which metabolize the adrenergic nerve mediators.[7,10-12]

The renal system is the main way for the excretion of metabolic wastes including urea (from the metabolism of the amino acids) and creatinine (Cr, from muscle creatine).[18] The Cr and blood urea nitrogen (BUN) are the metabolite materials representing the function of the renal system. Additionally, Cr is a product of breaking down of phosphocreatine which is used in skeletal muscle contractions. On the one hand, daily production of creatine and thus Cr depends on the muscle mass.[19] On the other hand, physical activity affects the renal function as well.[20]

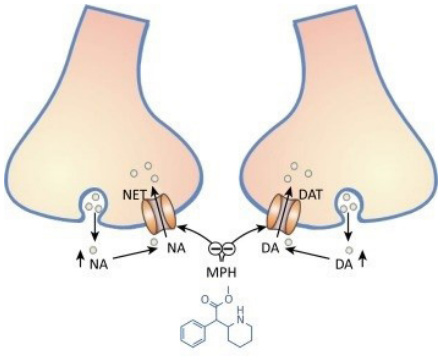

Figure 2. The mechanism of methylphenidate (MPH) effect in neurons: MPH binds to the monoamine transporters and inhibits the reuptake of neurotransmitters. The increase in neurotransmitters (i.e., DA and NA) in the synaptic cleft leads to an enhanced postsynaptic signal.

The injection of MPH into the isolated kidney significantly reduced the urine flow, glomerular filtration rate, and sodium transfer percentage while no significant differences were observed in urea, Cr, Cr clearance, as well as the fractional excretion of sodium and potassium.[21] On the other hand, 8-week aerobic exercise (AE) in the rats caused a significant decrease in the serum BUN and Cr levels, indicating an improvement in renal function following AE.[22,23] In addition, Rafati et al concluded that there was no significant difference in the serum BUN and Cr levels between the control and experimental groups after the eight-week of AE with 60-80% of $VO2_{max}$.[24]

Considering the increase in the therapeutic and non-therapeutic use of MPH, especially among the athletes and the conflicting results regarding the effect of physical activity on renal function,[11,25] the current study sought to assess the effects of MPH and AE on the renal function of the male rats.

Materials and Methods

Animals

The 3.5 month-old male Wistar rats with the average weight of 228±15 g were randomly assigned to eight groups (10 per each group). The rats were obtained from the Center of Laboratory Animals in Ahvaz Jundishapur University of Medical Sciences and were kept in polycarbonate cages (Tehran Avaya Danesh Company) at 23±2°C and a 12:12-hour dark-light cycle. The animals had unlimited access to commercial pellet food (Tehran Dam Pars Company) and tap water. One week before starting the research, the rats were acclimatized at these controlled environmental conditions.

Experimental Groups

The research groups included the control (Co, no AE and MPH administration), AE sham (AE, along with oral gavage of 1 mL distilled water), drug sham (D Sham, oral gavage of 1 mL of distilled water), AE, the effective dose of the drug (ED, 10 mg/kg),[12,17] three times the drug effective dose (TED, 30 mg/kg), AE–the effective dose of the drug (AE-ED), and AE–three times of effective dose of the drug (AE-TED) .

Drug

During the study (which lasted for 2 months), the rats in the drug effective dose group (10 mg/kg), three times of effective dose (30 mg/kg), AE-effective dose (10 mg/kg), and AE-three times of effective dose (30 mg/kg) were orally administrated with the drug. About half an hour after the drug was orally given by the gavage, some behaviors such as fast moving to the corners of the cage, standing on the legs, and increasing activity in the animals were observed in the drug recipient groups.[16] After the appearance of drug effects, the animals in the AE and AE-drug groups were transferred on a specific treadmill device to perform AE.

AE Protocol

AE sessions continued for two months including three sessions a week and 30 minutes in each session. The AE encompassed the warm-up (5 minutes at a speed of 16 m/min and the intensity of 50% of VO_{2max}), the main part of the exercise (30 minutes at a speed of 25 m/min, and the intensity of 78% VO_{2max}), and finally, cooling down (5 minutes at a speed of 16 m/min).[26-28]

Blood Sampling and Laboratory Analyses

After 24 hours of the last session, the animals were transferred to the anesthetic cabin (chamber) and then anesthetized and transferred to the surgery table. The abdomen and chest of the rats were opened using the surgical scissors, and the blood samples were taken from their left ventricle. BUN (GLDH method) and Cr (JAFFE method) serum levels were measured by diagnostic kits (Pars Azmun Company, Iran) using a spectrophotometer (Model SQ 4802 device, U.S UNICO Company).[29]

Statistical Analysis

The Kolmogorov-Smirnov test was conducted to assess the normalization of the data. Further, the analysis of variance (ANOVA) and post hoc Tukey tests were used for comparing the mean± standard deviation of BUN and Cr among the groups. Statistical analysis was performed by the SPSS software, version 21.

Results

As shown in Figure 3, the rats in this study have an average weight of 228±15 g.

Based on the results, a significant difference is found between the mean serum BUN among the groups ($F=15.442$ and $P=0.001$, Table 1).

Figure 4 illustrates the serum levels of BUN in different study groups. As shown, there is a significant increase in BUN in the AE-ED, AE-TED, and TED groups compared to the control (Co), AE Sham, and D Sham groups ($P=0.001$). Furthermore, a significant difference is detected between the AE and AE-TED groups ($P=0.004$).

In addition, the results of the ANOVA test show a significant difference in serum Cr levels among the groups ($F=50.692$ and $P=0.001$). Moreover, based on the results of the Tukey post-hoc test displayed in Figure 5, significant elevations are observed in serum Cr levels in ED, TED, AE-ED, and AE-TED groups compared to Co, AE Sham, and D Sham groups ($P=0.001$). Additionally, there is a significant difference in serum Cr levels between TED ($P=0.003$), AE-ED, and AE-TED groups compared to the AE group ($P=0.001$). Finally, the serum Cr levels demonstrate a significant difference between AE-ED and AE-TED groups compared to the ED group ($P=0.001$).

Table 1. Serum Levels of Blood Urea Nitrogen and Creatinine in Different Study Groups

Group	N	Cr (mg/dL) Mean±SD	Cr (mg/dL) Mean±SD
Control	10	21.1±2.8	0.359±0.03
AE Sham	10	21.5±1.1	0.353±0.03
D Sham	10	21.3±2.5	0.360±0.04
ED	10	22.3±1.3	0.473±0.04[a]
TED	10	24.8±2.4[a]	0.50±0.09[ab]
AE	10	23.9±2.6	0.40±0.02
AE-ED	10	27.1±3.1[ab]	0.580±0.08[abc]
AE-TED	10	28.7±2.5[ab]	0.610±0.07[abc]

AE: Aerobic exercise; D: Drug (methylphenidate); ED: Effective dose (10 mg/kg); TED: Three times effective dose (30 mg/kg).
[a] The mean difference is significant at the level of 0.05 with Control, AE Sham, and D Sham groups.
[b] The mean difference is significant at the level of 0.05 with AE group.
[c] The mean difference is significant at the level of 0.05 with ED group.

Discussion

The present study was implemented to determine the effect of MPH administration and AE on renal function

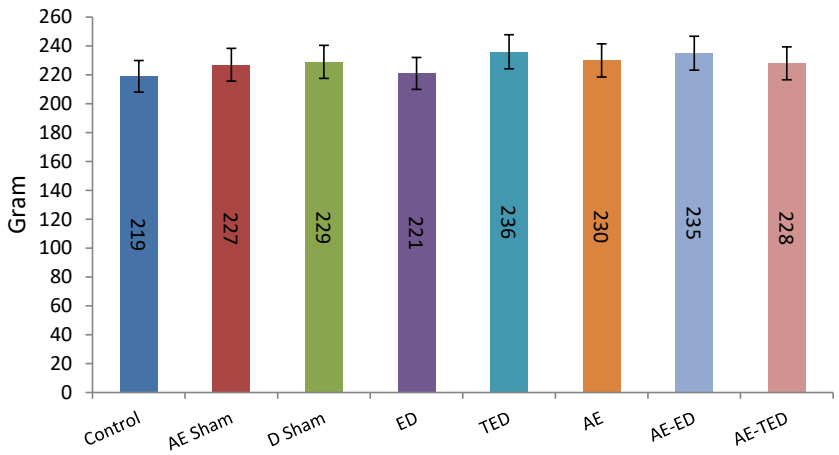

Figure 3. The mean weight of the rats in different experimental groups. AE: Aerobic exercise; D: Drug (methylphenidate); ED: Effective dose (10 mg/kg); TED: Three times effective dose (30 mg/kg).

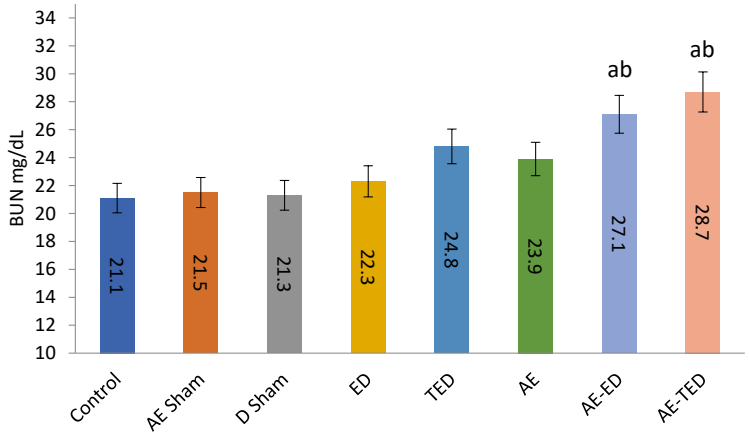

Figure 4. Serum levels of BUN in different study groups. a: The mean difference is significant at the level of 0.05 with Control, AE Sham, and D Sham groups; b: The mean difference is significant at the level of 0.05 with AE group; AE: Aerobic exercise; D: drug (methylphenidate); ED: Effective dose (10 mg/kg); TED: Three times effective dose (30 mg/kg).

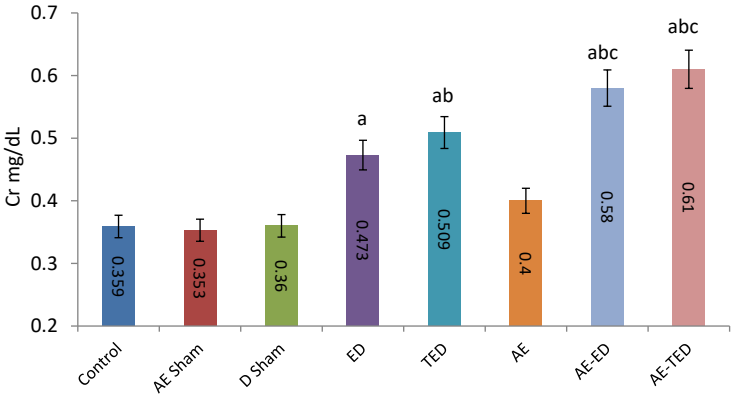

Figure 5. Serum levels of creatinine in different groups. a: The mean difference is significant at the level of 0.05 with Control, AE Sham, and D Sham groups; b: The mean difference is significant at the level of 0.05 with AE group; c: The mean difference is significant at the level of 0.05 with ED group; AE: Aerobic exercise; D: Drug (methylphenidate); ED: Effective dose (10 mg/kg); TED: Three times effective dose (30 mg/kg).

in the rats. The results indicated no significant differences in serum levels of serum Cr and BUN in Co, D Sh, and AE Sh groups compared to the AE group ($P=0.395$). Rafati et al reported that aerobic activity with an intensity of 60%-80% of maximum oxygen consumption after 8 weeks of running on treadmill failed to establish a significant difference on the serum BUN and Cr levels between control and experimental groups.[24] In addition, no significant difference was found in the serum Cr level after the exercise in elderly men with low activity compared to active young men.[30] Further, no significant change was detected in the Cr and BUN levels of elite cyclists after 12 weeks of exercise.[31] Similarly, based on the results of another study, the serum urea level of football players failed to change before, immediately after, and one hour after the exercise.[32] In addition, investigating the serum Cr and BUN levels in the rats represented no significant change after AE for 6 months with an intensity of 55%-65% of maximum heart rate.[33] Conversely, 8 weeks of AE in rats resulted in a significant decrease in the serum BUN and Cr levels compared to the inactive group.[22,23] Furthermore, Seiavoshy et al described that 10 weeks of resistance exercise in type 2 diabetic patients caused a significant decrease in BUN and Cr.[34] Overall, the findings of the above-mentioned studies indicate beneficial effects of physical activity, especially AE on serum BUN and Cr levels and renal function.[22,24,30-35]

On the other hand, several other studies reported an elevation of Cr and BUN after physical activity. For example, the results of one study demonstrated that physical activity with the maximum power increased the serum BUN and Cr levels of wrestlers.[20] Moreover, an eccentric resistance exercise session significantly increased the urea and Cr in the experimental group compared to the control group.[36] Additionally, significant increases were observed in Cr and BUN 24 hours after the marathon.[37] The significant increases in the Cr and BUN of the runners were reported by Adner et al, Andersen et al and Furan et al after the Boston Marathon Championships and the short-term exercises, respectively.[38-40]

These contradictory results may be due to the differences in the type, severities, and the duration of physical activities, as well as the differences in the subjects in terms of age, gender, and race. In addition, the sampling interval should be considered after physical activity.[34] However, in general, there is a direct relationship between the increase in intensity and the duration of physical activity and the increase in BUN and Cr serum levels with the severe and longer activities associated with higher serum levels of BUN and Cr.[34,40-42]

In the present study, significantly higher levels of BUN and Cr were observed in the groups which received ED and TED of MPH (P_{BUN}=0.003 and P_{Cr}=0.001) compared to the control groups (i.e., Co, AESh, and DSh). The pharmacokinetics of MPH drug and its bioavailability in humans are similar to those in the rats.[9,14,17] Significant tissue damage in the kidney of healthy rats was reported due to MPH consumption.[11] Further, the findings of Saliviano et al. indicated that MPH altered the renal function by reducing the glomerular activity, urinary flow, and sodium transfer, as well as renal toxicity.[21] Nymark et al in a case report claimed that an eighteen-year-old young impaired renal function due to the consumption of MPH.[43] Furthermore, a 32-year-old woman who abused MPH hydrochloride indicated complications such as the liver and renal toxicities, along with elevations in serum BUN and Cr levels.[44]

The results of the current study demonstrated significant increases in serum levels of BUN and Cr in the AE-ED and AE-TED groups compared to the control groups (i.e., Co, AESh, and DSh) and AE group (P_{Cr}=0.001 and P_{BUN}=0.001, respectively). Since taking MPH increased the level of interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), Motaghinejad et al suggested that doses of 10 and 20 mg/kg of MPH could produce nerve inflammation.[12] Moreover, MPH induced rapid increases in the pro-inflammatory cytokines of interleukin-6 (IL-6) and TNF-α.[45] In a study regarding understanding the effect of drug abuse in the brain of the mice, Gonçalves et al reported that the pro-inflammatory cytokines of IL-6 and TNF-α increased rapidly after taking 30 mg/kg of MPH.[46] Additionally, Réus et al concluded that 10 mg/kg of MPH can activate apoptotic cascade at the gene and protein levels in the cortex and the striatum of the rat brain.[47] Finally, increased levels of TNF-α in kidneys and TNF-α signaling through TNF-α receptor in renal endothelial cells were found to cause apoptosis through caspase-8 dependent pathway, and therefore, the reduced renal function following MPH administration may be due to the cell damage, as well as functional and structural changes in the kidneys.[48,49]

Conclusion

According to the results of this study, there was a possibility for nephrotoxicity induced by MPH even at the therapeutic dose of 10 mg/kg and higher doses. The possibility was even more severe when taking the drug, along with the physical activity. Therefore, studying the pharmacodynamics and the impacts of MPH on renal function, especially histological alternations are subject to further investigation.

Ethical Approval

This study was approved by the Ethics Committee of Science and Research Branch, Islamic Azad University, Iran (Code: IR.IAU.SRB.REC.1397.166).

Competing Interest

The authors of this article declare that there was no competing interest.

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