



Potential of Sodium-Glucose Cotransporter Inhibitors as Agents for Prevention of Ischemic and Reperfusion Kidney Injury

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Abstract: Sodium-glucose cotransporter 2 inhibitors are a relatively new class of glucose-lowering agents with significant advantages over other groups due to their good safety profile and protective effects on the cardiovascular system and kidneys. Today, the question of their ability to prevent and reduce the severity of acute kidney injury remains relevant. The primary objective of the study is to investigate the Potential of Sodium-Glucose Cotransporter Inhibitors as Agents for the Prevention of Ischemic and Reperfusion Kidney Injury. To gratify that objective, the experiment was performed on 80 Wistar line male rats. Acute kidney injury was simulated by reproducing a bilateral 40-minute renal ischemia-reperfusion. sodium-glucose cotransporter inhibitors were administered before surgery: dapagliflozin at doses of 0.5 mg/kg and 1 mg/kg, canagliflozin - 8.6 mg/kg and 25.7 mg/kg, empagliflozin - 1 mg/kg and 2 mg/kg. The renoprotective effects were evaluated after 72 hours based on the following parameters: serum creatinine and urea concentrations, glomerular filtration rate and fractional sodium excretion, as well as the level of renal microcirculation. Based on the results acquired, Preliminary administration of dapagliflozin, canagliflozin and empagliflozin led to a statistically significant decrease in the level of serum creatinine concentration and fractional sodium excretion, as well as an increase in the glomerular filtration rate, compared with the control group. The results demonstrated their dose-dependent effect and ability to improve the parameters of renal microcirculation. Plus, the results of the study demonstrate a high dose-dependent renoprotective potential of sodium-glucose cotransporter 2 inhibitors (dapagliflozin, canagliflozin and empagliflozin) on a model of bilateral renal ischemia-reperfusion. The results of this study can greatly contribute to the respective field.

Keywords: Glucose-Lowering Agents, Sodium-Glucose Cotransporter, Cardiovascular System, Kidneys.

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1. INTRODUCTION

According to the KDIGO guidelines, acute kidney injury (AKI) is defined as: an increase in serum creatinine concentration of ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 hours; or an increase in serum creatinine concentration of ≥ 1.5 times the baseline level (if known or suspected to have occurred during the previous 7 days); or urine volume <0.5 ml/kg/hour in 6 hours¹. Epidemiological studies demonstrate that acute kidney injury is a multifactorial syndrome and occurs in about 15% of hospitalized patients, reaching 43% after cardiothoracic surgery^{2,3}. Thus, more than 13 million people worldwide are diagnosed annually with an episode of AKI². It is assumed that there is also a significant part of patients with unregistered AKI due to the complexities of the diagnostic process and the lack of uniform criteria for making a diagnosis⁴. Incomplete or maladaptive recovery of kidney structures after an episode of acute kidney injury can lead to fibrosis of the renal structures, loss of renal cells and glomeruli, and the formation of pathological signaling pathways that contribute to the development and progression of chronic kidney disease^{5,6}. Ischemia is one of the universal damage factors affecting various organs and tissues⁷⁻¹³. The second most common pathogenetic variant of AKI is ischemic and reperfusion injury¹⁴. In this regard, pharmacological agents with cytoprotective^{7,15,16}, endothelioprotective^{17,18} and anti-inflammatory properties¹⁹ can become potential renoprotectors. Undoubtedly renoprotective properties of the sodium-glucose cotransporter 2 (SGLT-2) inhibitors are not in doubt²⁰⁻²², which creates advantages over other classes of glucose-lowering agent due to a reduced risk of drug interactions^{23,24}. However, their protective effects in acute kidney injury are not sufficiently studied: little experimental data have been obtained, and clinical studies demonstrate heterogeneous data on the ability of various SGLT-2 inhibitors to prevent the development of AKI²⁵⁻²⁸. Overall, as stated above, since Sodium-glucose cotransporter 2 inhibitors are a somewhat new class of glucose-lowering agents with substantial advantages over other groups owing to their desirable safety profile and protective impacts on the cardiovascular system and kidneys, this study was conducted to analyze the renoprotective properties of sodium-glucose cotransporter 2 inhibitors in modeling bilateral renal ischemia-reperfusion.

2. MATERIALS AND METHODS

The experiment was performed on 80 sexually mature male Wistar rats weighing 200-250 g, in compliance with ethical norms and principles "European Convention for the Protection of Vertebral Animals Used for Experimental and Other Scientific Purposes. CETS No. 123".

The animals were randomized into the following groups (n=10):

Group 1. Intact.

Group 2. Control group (modeling of renal ischemia-reperfusion).

Group 3. Dapagliflozin at a dose of 0.5 mg/kg + modeling of renal ischemia-reperfusion.

Group 4. Dapagliflozin at a dose of 1 mg/kg + modeling of renal ischemia-reperfusion.

Group 5. Canagliflozin at a dose of 8.6 mg/kg + modeling of renal ischemia-reperfusion.

Group 6. Canagliflozin at a dose of 25.7 mg/kg + modeling of renal ischemia-reperfusion.

Group 7. Empagliflozin at a dose of 1 mg/kg + modeling of renal ischemia-reperfusion.

Group 8. Empagliflozin at a dose of 2 mg/kg + modeling of renal ischemia-reperfusion.

2.1 Animals and Experimental Record

Modeling of renal ischemia-reperfusion was performed under anesthesia using chloral hydrate at a dose of 300 mg/kg according to the generally accepted method^{18,29,30}. The animals were placed in metabolic cages in 48 hours after removing the clamps, and urine was collected for 24 hours. After that, the microcirculation parameters were recorded, samples were taken for the subsequent study of the concentration of creatinine and sodium in the blood serum and urine, as well as the serum urea concentration.

2.2 Pharmacological Agents

Dapagliflozin was administered at doses of 0.5 mg/kg or 1 mg/kg 120 minutes before applying clamps to the renal pedicles; canagliflozin - at doses of 8.6 mg/kg or 25.7 mg/kg 90 minutes before applying clamps; empagliflozin - at doses of 1 mg/kg or 2 mg/kg 90 minutes before applying clamps. These pharmacological agents were administered intragastrically. The doses used are calculated taking into account the interspecies dose coefficients, the mode of administration is based on the pharmacokinetic properties of the agents.

2.3 Evaluation of The Functional State of the Kidneys

The glomerular filtration rate was calculated as follows, based on the clearance of endogenous creatinine, according to the formula (ml/min):

$$GFR = \frac{Cr(urea) \times V(urea)}{Cr(serum) \times t} (*)$$

* - $Cr(urea)$ - urine creatinine concentration ($\mu\text{mol/L}$); $V(urea)$ - urine volume (ml); $Cr(serum)$ - serum creatinine concentration ($\mu\text{mol/L}$); t - time (min).

2.4 Fractional Sodium Excretion Was Calculated Using the Following Formula (%)

$$FeNa = \frac{Na^+(urea) \times Cr(serum)}{Na^+(serum) \times Cr(urea)} (**)$$

* - $Na^+(urea)$ - urine sodium concentration; $Cr(serum)$ — serum creatinine concentration ($\mu\text{mol/L}$); $Na^+(serum)$ - serum sodium concentration; $Cr(urea)$ - urine creatinine concentration ($\mu\text{mol/L}$);

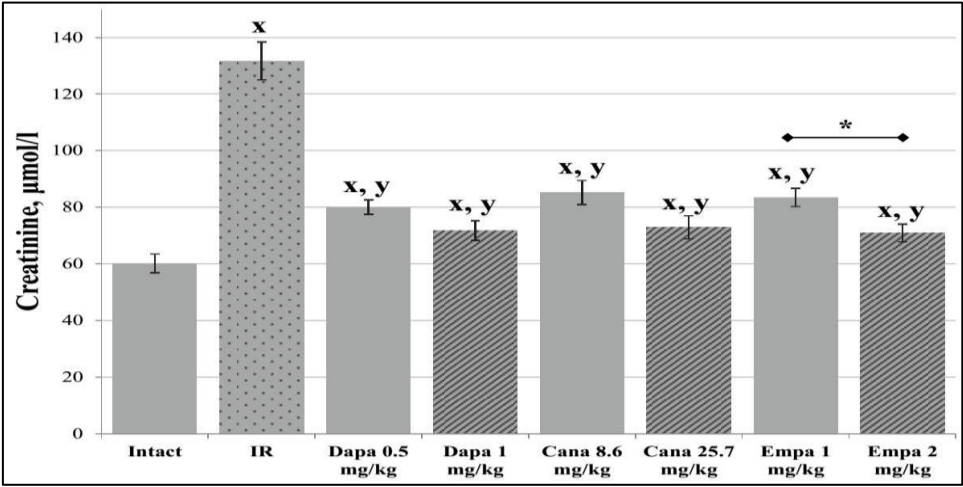
3. STATISTICAL ANALYSIS

The obtained data were checked for the normality of distribution using the Shapiro-Wilk test. In the case of a normal distribution, data were presented as average value (M) and standard error of the mean (m). Intergroup differences were analyzed using the Student's t-test; $p < 0.05$ indicated a statistically significant difference. Determination of serum concentration of creatinine, urea, sodium, as well as concentrations of sodium and creatinine in urine was performed using an automatic biochemical analyzer AU480. Microcirculation parameters were evaluated using the MPI00 hardware complex (Biopac System, Inc., USA) and the AcqKnowledge software. The measurement was performed using a TSD143 surface sensor applied to the middle third of

the kidney. Results are presented in perfusion units. Furthermore, the ethical committee of Belgorod State University approved this study and declared that there is no ethical issues.

4. RESULTS

Modeling of bilateral renal ischemia-reperfusion led to a predictable increase in serum creatinine concentration up to $131.7 \pm 6.7 \mu\text{mol/L}$, urea up to $9.15 \pm 0.25 \mu\text{mol/L}$. The glomerular filtration rate, respectively, decreased to $0.05 \pm 0.01 \text{ ml/min}$ and the fractional sodium excretion increased to $8.05 \pm 0.85\%$.

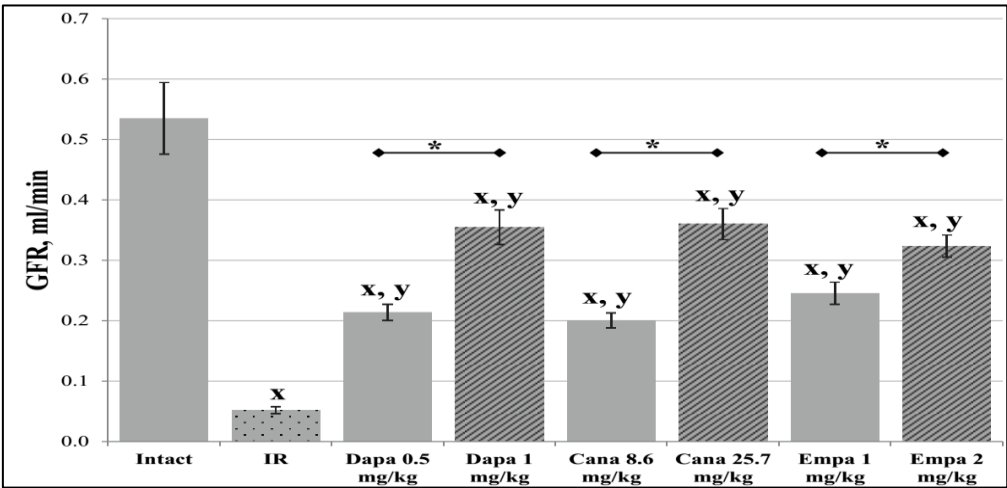


Note: x – $p < 0.05$ compared to intact; y – $p < 0.05$ compared to ischemia-reperfusion model; * – $p < 0.05$.

Fig 1: The effect of pre-administration of sodium-glucose cotransporter inhibitors on serum creatinine concentration in modeling renal ischemia-reperfusion.

Based on Figure 1, preliminary administration of dapagliflozin led to a dose-dependent realization of its renoprotective properties. This was confirmed by a decrease in creatinine concentration to $71.7 \pm 3.5 \mu\text{mol/L}$, a significant increase in GFR

to $0.35 \pm 0.03 \text{ ml/min}$, and a decrease in fractional sodium excretion to $1.9 \pm 0.26\%$ when using a dose of 1 mg/kg . All these parameters significantly differed from those of intact animals and the ischemia-reperfusion group ($p < 0.05$).

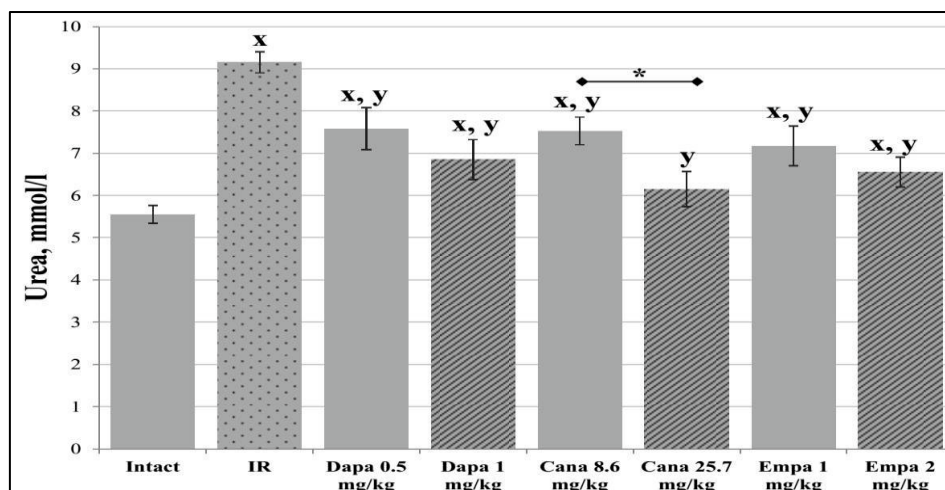


Note: x – $p < 0.05$ compared to intact; y – $p < 0.05$ compared to ischemia-reperfusion model; * – $p < 0.05$.

Fig 2: The effect of pre-administration of sodium-glucose cotransporter inhibitors on glomerular filtration rate in modeling renal ischemia-reperfusion.

Considering Figure 2, a similar dynamic was observed with the preliminary administration of canagliflozin and empagliflozin. Thus, the level of glomerular filtration rate and fractional sodium excretion during pharmacological correction with

canagliflozin at a dose of 25.7 mg/kg was $0.36 \pm 0.03 \text{ ml/min}$ and $1.67 \pm 0.2\%$, respectively, and with empagliflozin at a dose of 2 mg/kg was $0.32 \pm 0.02 \text{ ml/min}$ and $1.53 \pm 0.14\%$.

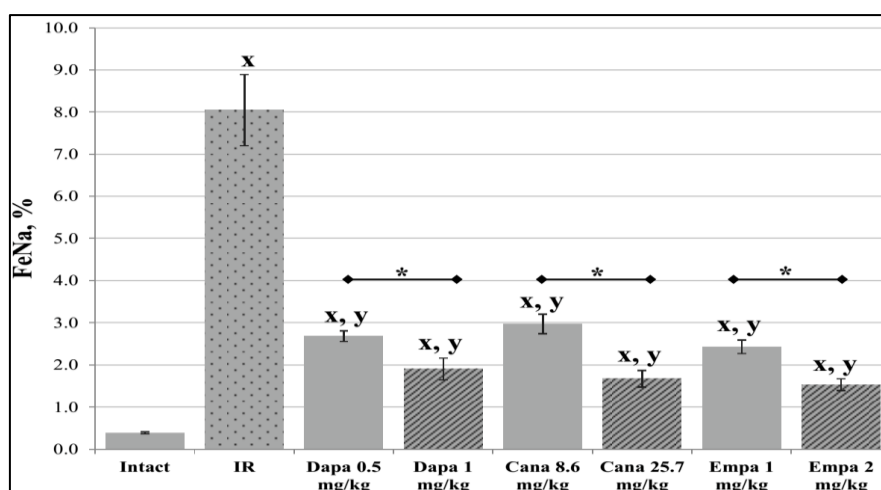


Note: x – $p < 0.05$ compared to intact; y – $p < 0.05$ compared to ischemia-reperfusion model; * – $p < 0.05$.

Fig 3: The effect of pre-administration of sodium-glucose cotransporter inhibitors on serum urea concentration in modeling renal ischemia-reperfusion.

Observing Figure 3, the dynamics of serum creatinine concentration upon preliminary administration of canagliflozin at a dose of 25.7 mg/kg and empagliflozin at a dose of 2 mg/kg also confirmed the hypothesis of their protective effects in

renal ischemia-reperfusion, decreasing to $72.9 \pm 4.1 \mu\text{mol/L}$ and $70.9 \pm 3.1 \mu\text{mol/L}$ respectively ($p < 0.05$ in comparison with the parameters of intact animals and the control group).



Note: x – $p < 0.05$ compared to intact; y – $p < 0.05$ compared to ischemia-reperfusion model; * – $p < 0.05$.

Fig 4: The effect of pre-administration of sodium-glucose cotransporter inhibitors on fractional sodium excretion in modeling renal ischemia-reperfusion.

Table 1. The effect of pre-administration of sodium-glucose cotransporter inhibitors on renal microcirculation level in modeling renal ischemia-reperfusion ($M \pm m$, PU).

Experimental group (n=10)	Microcirculation level
Intact	913.8±70.9
Ischemia-reperfusion model	345.1±26.7 ^x
Dapagliflosine correction, 0.5 mg/kg	493.2±45.8 ^{x,y}
Dapagliflosine correction, 1 mg/kg	656.1±32.6 ^{x,y}
Canagliflosine correction, 8.6 mg/kg	530.4±63.1 ^{x,y}
Canagliflosine correction, 27.5 mg/kg	700.4±43.3 ^{x,y}
Empagliflosine correction, 1 mg/kg	486.6±64.9 ^{x,y}
Empagliflosine correction, 2 mg/kg	676±57.1 ^{x,y}

Note: x – $p < 0.05$ compared to intact; y – $p < 0.05$ compared to ischemia-reperfusion model; * – $p < 0.05$.

Table 1 illustrates the effect of pre-administration of sodium-glucose cotransporter inhibitors on renal microcirculation level in modeling renal ischemia-reperfusion ($M \pm m$, PU). And Figure 4 depicts the effect of pre-administration of sodium-glucose cotransporter inhibitors on fractional sodium excretion in modeling renal ischemia-reperfusion. Given Figure 4 and table 1, the microcirculation parameters in the control group decreased by more than 2.5 times reaching 345.1 ± 26.7 PU in 72 hours after removing the clamps from the renal pedicles. Preliminary administration of dapagliflozin at a dose of 1 mg/kg, canagliflozin at a dose of 25.7 mg/kg, and empagliflozin at a dose of 2 mg/kg led to a significant improvement in the state of the microvasculature in the kidneys: parameters increased to 656.1 ± 32.6 PU, 700.4 ± 43.3 PU, and 676 ± 57.1 PE, respectively. The use of lower doses also had protective effects, but their severity was significantly lower.

5. DISCUSSION

For a long time, ischemic injury was the main cause of AKI ³¹. Unfortunately, despite the increase in the pool of therapeutic options and a sufficient amount of experimental data, there is currently no highly effective therapy for the prevention and treatment of AKI ³². Therefore, the search for pharmacological agents capable of preventing the development and reducing the severity of ischemic and reperfusion injuries in various tissues and organs, including the kidneys, is undoubtedly one of the most important tasks of pharmacology. The renal ischemia-reperfusion model is one of the most common experimental models of acute kidney injury, as it allows simulating various clinical situations, including kidney damage during transplantation, organ-preserving kidney surgery and cardiac surgery. Modeling of bilateral renal ischemia followed by reperfusion for 72 hours was characterized by the registration of changes comparable to the results of other authors: an increase in serum creatinine and urea concentrations, a decrease in GFR, and an increase in fractional sodium excretion ^{18, 29, 30}. Sodium-glucose cotransporter inhibitors have demonstrated their renoprotective properties in patients with diabetes mellitus and/or chronic kidney disease ³³, as well as in modeling these conditions in laboratory animals ^{34,35}. One of the key mechanisms for the realization of their protective effects, researchers call the activation of the reverse tubuloglomerular connection, which leads to a decrease in hyperfiltration, one of the key pathogenetic links of kidney injury in diabetes mellitus, chronic kidney disease, and arterial hypertension ^{17, 28}. On the contrary, tubuloglomerular feedback is one of the components damaging kidney tissue in ischemic and reperfusion injuries, as it leads to glomerular vasospasm, which makes a significant contribution to the decrease in GFR in AKI ²⁹. In this regard, it was suggested that SGLT-2 inhibitors may increase the risk of developing AKI, which has been demonstrated in some studies ²⁸. However, subsequent systematic reviews and meta-analyses, on the contrary, confirmed the hypothesis of reducing the risks of AKI in patients taking SGLT-2 inhibitors ^{25,26}. Information on the protective effects of SGLT-2 inhibitors was obtained in

experimental modeling of ischemic and reperfusion injuries of various organs. Administered before ischemia dapagliflozin at a dose of 1 mg/kg provided cardioprotection: the frequency of arrhythmias, the size of the infarction, mitochondrial dysfunction decreased, and the function of the left ventricle improved ²⁰. Empagliflozin at a dose of 10 mg/kg reduced the amount of brain tissue damage in rats along with suppression of cerebral oxidative stress, a decrease in inflammatory and apoptotic markers in the brain tissues of rats with hyperglycemia, and modeling of bilateral occlusion of the common carotid artery for 30 minutes, followed by 24-hour reperfusion ¹¹. A single intravenous bolus of canagliflozin in 5 minutes after the start of ligation of the carotid artery branch significantly reduced the size of myocardial infarction, as well as the levels of troponin-T in the blood serum, and also restored the systolic and diastolic function of the left ventricle and preserved its mechanoenergetics ^{17,19}.

6. CONCLUSION

In conclusion, considering the importance of Sodium-glucose cotransporter 2 inhibitors, this study intended to analyze the renoprotective properties of sodium-glucose cotransporter 2 inhibitors in modeling bilateral renal ischemia-reperfusion. To that end, the experiment was performed on 80 Wistar line male rats. The results of this experiment demonstrate the protective effects of representatives of this group of pharmacological agents, dapagliflozin, canagliflozin, empagliflozin, which are most clearly manifested when using higher doses: 1 mg/kg, 25.7 mg/kg and 2 mg/kg, respectively. These conclusions were obtained based on the serum creatinine and urea concentrations, glomerular filtration rate and fractional sodium excretion, which statistically significantly differed from those of the control group ($p < 0.05$). The positive effect of SGLT-2 inhibitors on the parameters of microcirculation in the renal tissue has also been demonstrated. The results of the study demonstrate a high dose-dependent renoprotective potential of pre-administration of sodium-glucose cotransporter 2 inhibitors (dapagliflozin, canagliflozin and empagliflozin) in modeling bilateral renal ischemia-reperfusion. This was evidenced by a decrease in serum creatinine and urea concentrations, an increase in GFR, a decrease in fractional sodium excretion, and an increase in microcirculation in kidney tissue. Regarding future studies, it can be recommended that mechanistic studies shall elucidate the potential relation between the infarct size-lowering impact of SGLT2 inhibitors and the intact organ system.

7. AUTHORS CONTRIBUTION

V.Y.P., M.V.P., I.B.K., and D.A.K. carried out the experiment. I.B.K., and D.A.K. helped supervise the project. V.Y.P. and M.V.P. conceived and planned the experiments. All authors discussed the results and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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