



# Investigation of Kisspeptin Role in Experimental Kidney Ischemia/Reperfusion Injury

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## Abstract

**Introduction:** Kisspeptin is biologically active peptide encoded by the KISS1 gene that is structurally found in the kidney tubule, collecting duct and vein smooth muscle cells.

**Aim:** We aimed to investigate the role of kisspeptin in kidney function and renal pathophysiology in experimental kidney ischemia/reperfusion (I/R) injury.

**Materials and methods:** Male Sprague-Dawley rats were divided into control and I/R groups (n=8). Both kidney vessels of I/R group rats were clamped and subjected to ischemia for 60 minutes and reperfusion for 48 hours. After the reperfusion period blood samples and kidney tissue were collected under anesthesia.

**Results:** Levels of urea, creatinine ( $p<0.01$ ) in serum, Kim-1 in urine ( $p<0.05$ ) were increased, creatinine clearance, aldosterone and ANG II levels in serum were decreased in the I/R group compared with the Control group ( $p<0.05$ ). Kidney kisspeptin levels decreased and urine kisspeptin levels increased ( $p<0.05$ ).

**Conclusions:** The present study has shown that the levels of kisspeptin change in kidney damage and thus the kisspeptin may play a role in the regulation of renal function and in the pathophysiology of acute kidney injury.

## Keywords

acute kidney injury, ischemia/reperfusion, kisspeptin, peptide

## INTRODUCTION

Acute kidney injury (AKI) is a disease characterized by a decrease in urinary output, an increase in serum creatinine and nitrogenous products, and a reduced ability of the kidney to regulate the balance of fluid and electrolyte due to sudden loss of renal function.<sup>1</sup> Today, AKI remains an important clinical problem, despite new research and new advances in treatment.<sup>2</sup> Ischemia reperfusion (I/R) is one of the most important causes of AKI induced by various etiological factors. AKI developed with I/R injury affecting approximately 13.3 million patients per year continue to be one of the social public health problems with high morbidity,

mortality and health costs. This situation occurs in various clinical situations such as kidney transplantation, cardiovascular surgery, sepsis, and shock.<sup>3</sup> During ischemia, there are some changes in the kidney tubules, glomerulus, and veins at the cellular level. Reperfusion is necessary for the survival of ischemic kidney tissue, but leads to additional damage.<sup>4</sup> Reactive oxygen species (ROS), reactive nitrogen species (RNS), purine metabolites, vasoactive peptides (angiotensin II (Ang II)), angiotensin converting enzyme (ACE), and neuropeptides (orexin-A, neuropeptide Y, endothelin, urotensin II) are involved.<sup>5</sup>

Kisspeptin is a neuropeptide encoded by the KISS1 gene by activating GPR54 receptor. It is known that the

kisspeptin and receptors are excreted from the central nervous system, heart, ovary and placenta. In addition, recent studies have shown their existence in kidney tubule cells, collecting duct cells and vascular smooth muscle cells.<sup>6</sup> Kisspeptin is reported to stimulate sexual development, suppress tumor metastasis, increase insulin secretion, regulate kidney development, stimulate aldosterone release and therefore causing vasoconstriction.<sup>7-9</sup> The first evidence that kisspeptin plays an important role in kidney function has been given by Shoji I et al.<sup>6</sup> The researchers report that kisspeptin and KISS1 (GPR54) receptors are found in tubular cells, collecting duct cells and vessels of smooth muscle cells in rat kidneys. It was found that KISS1R protein levels decreased significantly in chronic renal failure. In addition, deletion of the KISS1 receptor caused a defect in embryonic branching morphogenesis, reduced glomerular development and decreased glomerular count in adult kidney, resulting in renal failure.<sup>10</sup>

All of these findings suggest that kisspeptin may have a role for kidney function. However, the importance and role of kisspeptin in ischemic AKI remains unclear. In the light of what we have said above, we aimed to investigate the association of kidney function, Ang II, ACE, and aldosterone with kisspeptin in experimental kidney I/R injury.

## MATERIALS AND METHODS

### Animals

In this study, 16 male Sprague-Dawley rats weighing 300-350 g each were used. Rats were randomly divided into 2 equal groups (n=8). Food and water were provided ad libitum to the rats that were kept under standard laboratory conditions (22±1°C and 12 hours light/dark cycle). The study was approved by the Local Ethics Committee of the Animal Experiments of Trakya University (2016/13).

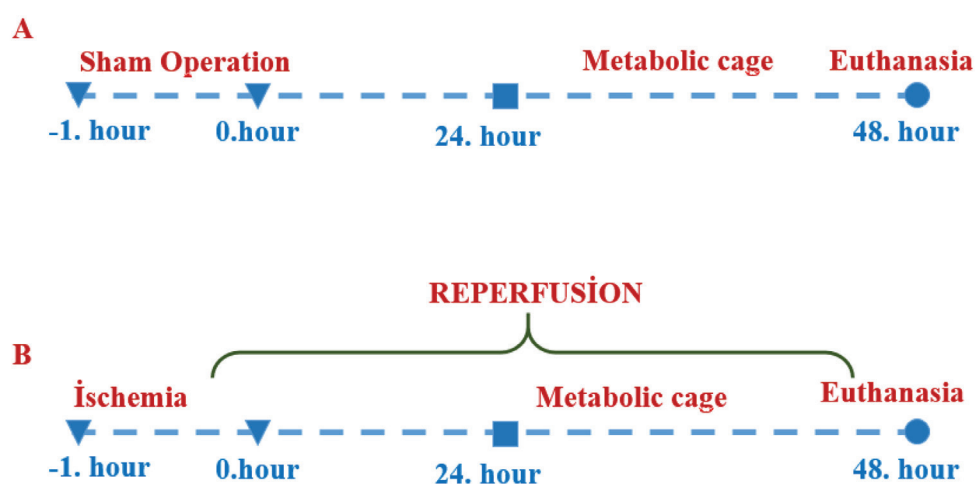
### Experimental Design

Rats were anesthetized by intramuscular injection with the 10 mg/kg of xylazine (Rompun, Bayer, Turkey) and 90 mg/kg ketamine (Ketasol, Richterphar AG, Wels-Austria). After anesthesia, abdominal areas of the rats placed on the 37°C heated experimental table and were shaved and the midline was incised. Both kidney vessels were removed. The blood flow in renal vessels of the I/R group were occluded by applying atraumatic microvascular clamp (FST, 85 g, USA) for 60 minutes. At the end of ischemic period, clamps were removed and reperfusion was performed for 48 hours. During the experiment, sterile physiological saline equivalent of 5% of body weight at 37°C were given to abdomen in order to compensate the fluid loss. The same surgical procedure except clamping the vessels was done on the animals in Control group. The experimental design is shown in **Fig. 1**.

At 24 hours of reperfusion, all rats were placed in metabolic cages and urine specimens were collected for 24 hours. At 48 hours of reperfusion, blood and kidney samples were taken under anesthesia by administering 10 mg of rompun and 50 mg/kg ketamine to the rats. After the kidneys were removed, they were divided into 2 pieces longitudinally; one part was homogenized, the other part was removed with the left kidney until the analysis was performed at -80°C. Blood (after waiting for 2 hours) and urine samples (direct) were centrifuged at 3000 rpm in a refrigerated centrifuge at 3000 rpm for 15 min for blood samples, 20 min for urine samples and placed at -80°C until analyzed by taking into eppendorf tubes.

### Biochemical studies at the kidney level

In our study levels of red-GSH, ox-GSH, NO and kisspeptin in kidney tissue were measured using ELISA red-GSH and ox-GSH (Mybiosource, Inc., USA), NO (Enzo Life Sciences, Inc., USA) and kisspeptin (Elabscience, Biotech Co. Ltd,



**Figure 1.** Experimental design of the control group (A) and I/R group (B).

USA) following the manufacturer's protocol. Kidney MDA content was determined by spectrophotometric methods.

### Biochemical studies at serum level

Serum NO (Enzo Life Sciences, Inc., USA), Arginine (Mybiosource, Inc., USA), aldosterone, ACE, Ang II, and kisspeptin (Elabscience, Biotech Co. Ltd, USA) levels was determined according to manufacturer's instruction.

Serum sodium (Na<sup>+</sup>), potassium (K<sup>+</sup>), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK) activities, urea and creatinine levels were determined by autoanalyzer (Kamelab Prime 60i, Finland).

### Biochemical studies at urine level

Urine Kim 1 (Mybiosource, Inc., USA), NO (Enzo Life Sciences, Inc., USA), microalbuminuria and kisspeptin (Elabscience-Biotech Co. Ltd, USA) levels were measured by ELISA kit in our laboratory. Creatinine, Na<sup>+</sup>, and K<sup>+</sup> levels in the urine were measured by an autoanalyzer (Konelab Prime 60i, Finland).

### Statistical analysis

Findings in our study were expressed as mean ± standard deviation. The Mann-Whitney U test was used to compare the differences between the groups.  $p < 0.05$  was considered as statistically significant. SPSS 20.0 (License No: 10240642) package program was used for statistical analysis.

## RESULTS

### Biochemical study findings at the kidney level

In our study, oxidative stress was evaluated with oxidative stress markers such as MDA, red-GSH, ox-GSH, NO in the kidney. There was a significant increase in oxidative stress markers of renal tissues of I/R group rats compared with the control group in the levels of red-GSH ( $p < 0.001$ ), ox-

GSH ( $p < 0.05$ ), NO ( $p < 0.01$ ), while in kisspeptin ( $p < 0.001$ ) levels were decreased and MDA ( $p > 0.05$ ) levels was not statistically significant (Table 1).

### Biochemical study findings at serum level

In our study, we found that Serum ALT ( $p < 0.001$ ), AST ( $p < 0.01$ ), urea ( $p < 0.001$ ), creatinine ( $p < 0.001$ ), ACE ( $p < 0.001$ ) and NO ( $p < 0.05$ ) were significantly increased in the I/R group as compared with Control group data. Levels of aldosterone ( $p < 0.01$ ), Ang II ( $p < 0.05$ ) and arginine ( $p < 0.001$ ) were decreased, and kisspeptin, Na<sup>+</sup>, K<sup>+</sup> levels in serum samples was no statistically significant difference for the I/R group when compared with Control group (Table 2).

### Biochemical study findings at urine level

The findings of our study showed that Na<sup>+</sup>, K<sup>+</sup>, creatinine, creatinine clearance ( $p < 0.001$ ) levels decreased, while FeNa, NO, Kim-1, urine volume ( $p < 0.001$ ) and kisspeptin levels ( $p < 0.01$ ) in urine samples were significantly increased for the I/R group as compared with Control group (Table 3).

## DISCUSSION

AKI, a major problem of current medicine, is a common and potentially life-threatening condition in recent times. One of the most common causes of AKI, known as a complex disease, is I/R injury. Currently, there are no specific treatments for patients with ABI due to I/R other than kidney transplantation and supportive treatments. Therefore, new treatment strategies are needed to preserve end-stage renal failure and renal dysfunction.<sup>11</sup> Many experimental studies have been carried out by the AKI models on experimental animals aimed at closing this gap in treatment. In our study, we used a commonly used model: AKI model which is done by bilateral kidney I/R. The duration of ischemia plays a very important role in the development of end-stage kidney damage. Today, there are many studies that apply I/R at different times to create AKI. In the experimental I/R model, it was stated that ischemia should be applied to the kidney vessels for 60 minutes in order to

**Table 1.** Biochemical results of experimental groups in the kidney tissue

Parameters	Control Group	I/R Group	p value
MDA (nmol/g tissue)	0.99±0.29	1.26±0.56	>0.05
red-GSH (ng/mg protein)	0.06±0.004	0.09±0.006	<0.001
ox-GSH (pg/mg protein)	67.95±55.38	146.80±14.76	<0.05
Arginine (µmol/mg protein)	0.64±0.51	0.56±0.36	>0.05
NO (µmol/mg protein)	14.76±0.94	13.17±0.75	<0.01
Kisspeptin (pg/mg protein)	368.34±23.34	116.89±46.44	<0.001

Data are presented as mean±SD. I/R group: Ischemia/Reperfusion group; MDA: malondialdehyde; red-GSH: reduced glutathione; ox-GSH: oxidized glutathione; NO: nitric oxide

**Table 2.** Biochemical results of experimental groups in the serum

Parameters	Control Group	I/R Group	p value
AST (U/L)	293.75±42.56	453.13±85.04	<0.01
ALT (U/L)	51.38±5.24	89.88±43.00	<0.001
CK (U/L)	2105.75±513.09	1647.00±523.63	>0.05
Urea (mg/dl)	36.63±4.53	375.75±65.57	<0.001
Creatinine (mg/dl)	0.29±0.35	4.13±1.25	<0.001
SNa (mmol/L)	131.38±8.77	127.88±9.85	>0.05
SK (mmol/L)	4.94±0.67	5.28±1.22	>0.05
Aldosterone (pg/mL)	2909.79±3162.41	631.15±210.86	<0.01
ACE (pg/mL)	6.65±1.44	32.52 ±11.16	<0.001
Ang II (pg/mL)	1013.53±641.95	449.12±108.52	<0.05
Kisspeptin (pg/mL)	99.64±17.05	91.46±15.60	>0.05
Arginine (µmol/L)	72.52±15.21	30.41±8.59	<0.001
SNO (µmol/L)	46.61±9.45	59.70±12.06	<0.05

Data are presented as mean±SD. I/R group: Ischemia/Reperfusion group; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK: creatine phosphokinase; SNa: serum sodium; SK: serum potassium; ACE: angiotensin converting enzyme; Ang II: angiotensin II; SNO: serum nitric oxide

**Table 3.** Biochemical results of experimental groups in the urine

Parameters	Control Group	I/R Group	p value
UNa (mmol/L)	139.00±30.58	41.00±12.46	<0.001
UK (mmol/L)	291.88±59.38	44.75±9.10	<0.001
Creatinine (mg/dl)	108.13±22.86	17.98±7.88	<0.001
Creatinine clearance (ml/dk)	2.76±0.61	0.15±0.10	<0.001
FeNa%	0.29±0.08	11.67±11.62	<0.001
FeK%	16.08±3.98	226.50±98.12	<0.01
UNO (µmol/L)	10.85±2.19	68.16±11.44	<0.001
KIM-1 (ng/mL)	0.04±0.02	0.38±0.05	<0.001
Kisspeptin (pg/mL)	44.87±17.61	101.39±37.37	<0.01
Urine volume (ml)	10.73 ±2.35	39.88 ±5.93	<0.001

Data are presented as mean±SD. I/R Group: Ischemia/Reperfusion group; UNa: urine sodium; UK: urine potassium; FeNa: fractional excretion of sodium; FeK: fractional excretion of potassium. UNO: urine nitric oxide; KIM-1: kidney injury molecule-1

cause damage to both the distal and proximal tubules.<sup>12</sup> Therefore, we chose 60 minutes of ischemia and 48 hours of reperfusion. In the experimental AKI model which we created by applying 60 minutes of ischemia and 48 hours of reperfusion to both kidney vessels of rats, it was observed that KIM 1 levels and oxidative stress increased as a biomarker of renal proximal tubule injury. These data show that the AKI model is formed by I/R.

Renal I/R injury usually results in damage and dysfunction in kidney tubules and glomerules. An increase in Kim 1 protein in the process is considered as a marker of proximal tubule damage in the kidney. It has been reported that a significant increase in urine Kim 1 level was observed in the I/R group compared to the control group in the AKI models formed by renal I/R injury in literature studies.<sup>13,14</sup> The increase in urine Kim 1 level which indicates the oc-

currence of kidney damage in the I/R group after 60 minutes of ischemia and 48 hours of reperfusion was similar to the results of the study described above.

In our study, increase in serum urea and serum creatinine levels and decrease in creatinine clearance in I/R group rats indicate that glomerular function is impaired. In addition, there was an increase in serum AST and ALT levels, in fractional Na<sup>+</sup> and fractional K<sup>+</sup> excretion, an indicator of renal tubular dysfunction in I/R group rats. Increase of AST enzymes which are present in kidney tubule cells, in serum shows tubular damage, whereas increase in FeNa levels indicates deterioration of tubular function. Furthermore, an increase in the level of KIM1 confirms the formation of proximal tubule damage. These findings are similar to those found by Chatterjee PK et al.<sup>15</sup> and Malek M et al.<sup>16</sup>

Nitric oxide is formed during the conversion of L-arginine to L-sitruilin via nitric oxide synthases (NOS). It is known that kidneys play a role in many events such as regulating NO glomerular hemodynamics, regulation of mitochondrial respiration, tubuloglomerular feedback mechanism, excretion of Na<sup>+</sup>, Cl<sup>-</sup>, and H<sub>2</sub>O, including renin secretion.<sup>17</sup> It has been reported that arginine administration in renal I/R injury protects the kidney from toxic and ischemic damage.<sup>18</sup> A significant increase in renal NO levels, serum NO and urinary NO levels was observed in the rat model of acute renal damage induced by experimental I/R injury. Serum arginine levels decreased in the I/R group and no significant changes were observed in the renal arginine levels. These results are consistent with the results obtained by Koç M et al.<sup>19</sup>

During ischemia, free radicals cause damage in cells. This affects the lipids in the cell membrane initially. When the lipids in the cell membrane are oxidized by free radicals, a number of reactions start and the final product is MDA. Lipid peroxidation causes degradation of membrane permeability and thus cell destruction. These events, which occur in tubular cells, are also known to be one of the major causes of kidney damage. It has been reported that MDA levels in the I/R group are higher in the AKI models formed by renal I/R injury than in the control group.<sup>20,21</sup> In our study, we found that MDA level was higher in the I/R group than in the control group when there was no statistically significant difference between the control group and the I/R group. In our study, reperfusion after 60 minutes of ischemia and 48 hours of reperfusion may be a cause of no significant difference in MDA level. These results indicate that oxidative damage is increased in the I/R group.

After the oxidative damage that occurs in the I/R period, antioxidant enzymes such as GSH, catalase, glutathione peroxidase, superoxide dismutase get activated. In many similar studies like that of Bağcıoğlu M, et al.<sup>20</sup> it was reported that the rats subjected to I/R compared to the control group showed a decrease in renal red – GSH levels and an increase in ox – GSH levels. In our study, it was determined that the red – GSH level increased in an interesting way as the ox – GSH levels in the rat kidneys that I/R were administered increased in accordance with the above study results. This difference in our findings may be due to the difference in I/R duration that we apply to the rat kidneys.

Recently, it has been reported that the kisspeptin is directly and indirectly related to the physiology and pathophysiology of the urogenital system.<sup>22</sup> Yi et al. (2010) have shown that kisspeptin, known to regulate kidney development and morphogenesis, controls also the expression of bmp7, which plays an important role in kidney development and repair of tubular damage in renal diseases.<sup>10</sup> However, there is currently limited information about the association of the various pathological states of kidney and kidney with kisspeptin, and the physiopathological role of kisspeptin in acute kidney injury is unknown.

Our literature review is the first to investigate the change in kisspeptin in AKI. We assessed changes in the expression

of the kisspeptin in response to acute renal injury due to ischemia reperfusion in our study. As a result of the study, the kidney kisspeptin levels and urine kisspeptin levels were increased in the experimental group of experimental acute renal failure (I/R group). There was no significant change in serum KISS levels. In the model of chronic renal failure developed by applying 5/6 neurectomy; compared with the control group, the levels of the kisspeptin mRNA in the ischemic group did not show any significant difference at 3 days, but decreased at 56 days. In addition, it was reported that there was a significant increase in the polypeptide receptor immunoreactivity on the 56<sup>th</sup> day. mRNA levels of kisspeptin receptors in the kidneys; It was reported that there was a significant increase on days 14 and 56 when there was no significant difference on day 3. In this study, in which chronic kidney damage was developed; it has been reported that kisspeptin and its receptors play a role in the regulation of renal function and in the pathophysiology of chronic renal failure.<sup>6</sup> The reason for not having a significant difference in serum kisspeptin levels in our model may be due to the low reperfusion period.

It has been reported that during the pregnancy period, the concentration of kisspeptin at the dramatic level increases, eventually increasing the level of aldosterone in the fetal adrenal gland.<sup>23</sup> It has also been reported that kisspeptin induces aldosterone secretion by increasing Ang II level. In our study, the decrease in serum kisspeptin levels in the I/R group was not significant, but serum Ang II and aldosterone levels were significantly decreased. A significant increase in ACE level was observed.

Nowadays, the RAAS system plays an important role in the progress of I/R injury. There are many studies in the literature about RAAS system and I/R relationship. It has been reported significantly elevated serum Aldosterone levels in the I/R group compared to the Control group in their studies of 20 min ischemia and 24 h reperfusion, and 45 minutes of ischemia and 24 hours of reperfusion.<sup>24,25</sup> Efrati et al.<sup>26</sup> (2012) have reported that kidney and serum Ang II levels were significantly reduced in the I/R group where they were subjected to reperfusion for up to 24 hours, in their study of 60 ischemia and reperfusion at various times. Da Silveira et al.<sup>27</sup> (2010) reported a reduction in renal ACE levels compared to the Control group in the IR groups that received 45 minutes of ischemia and reperfusion at different time periods. In the results of our study, which was differentiated from the above-mentioned studies by different I/R period, serum Aldosterone showed different results with increase of serum ACE levels and decrease of serum ANG II levels. Ten et al.<sup>28</sup> (2010) reported that administration of central kisspeptin in anesthetized rats increased plasma antidiuretic hormone levels, reducing Na<sup>+</sup> excretion and urine volume. When we compare the findings of our study with the literature, it can be concluded that the lack of significant difference in serum levels of kisspeptin it may be the result of a short reperfusion period.

## CONCLUSION

Evaluating the results of this study and the relevant literature we can conclude that kisspeptin may play a role in the pathophysiology of experimental I/R injury. We think that kidney mRNA concentration of kisspeptin and mRNA levels of kisspeptin receptors should be examined during different reperfusion periods in order to investigate the relationship and effect of kisspeptin with renal function and renal damage. We also think that there is a need for more comprehensive studies of kidney blood flow, renal function, parameters showing the degree of oxidative damage and effects on NO metabolism by administering kisspeptin at different doses.

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# Изучение роли Кисспептина при экспериментальной почечной недостаточности вследствие ишемии / реперфузии.

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## Абстракт

**Введение:** Кисспептин - это биологически активный пептин, кодируемый геном KISS1, который структурно обнаруживается в канальцах почек, собирательных протоках и клубочках, а также в клетках венозной гладкой мускулатуры.

**Цель:** Мы стремились исследовать роль кисспептина в функции почек и патофизиологии при экспериментальной почечной недостаточности вследствие ишемии / реперфузии.

**Материалы и методы:** Самцов крыс Sprague-Dawley разделили на контрольную и И / Р группы (n = 8). Оба почечных сосуда крыс в группе И / Р были зажаты и подвергнуты ишемии в течение 60 минут и реперфузии в течение 48 часов. После периода реперфузии были взяты образцы крови и почечной ткани под анестезией.

**Результаты:** Уровни мочевины и креатинина в сыворотке крови (p <0,01), Kim-1 в моче (p <0,05) были увеличены, клиренс креатинина, альдостерон и уровни ANG II в сыворотке были снижены в группе И / Р по сравнению с контрольной группой (p <0,05). Почечный уровень кисспептина был снижен, а уровни в моче увеличились (p <0,05).

**Выводы:** Настоящее исследование показало, что уровни кисспептина изменяются при почечной недостаточности и, таким образом, кисспептин может играть роль в регуляции почечной функции и в патофизиологии острой почечной недостаточности.

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## Ключевые слова

кисспептин, острая почечная недостаточность, ишемия / реперфузия, пептид

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