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Renoprotective effects of GABA on ischemia/reperfusion- induced renal injury in hyperglycemic male and female rats

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Original Article

Abstract

Introduction: Acute kidney injury (AKI) has been known as a complex clinical complication in diabetic patients. The main cause of AKI is ischemia/reperfusion injury (IRI). This study was designed to investigate the protective effects of GABA on renal IRI in hyperglycemic female and male rats.

Methods: Sixty STZ induced diabetic male and female Wistar rats were categorized in 10 groups (5 female &5 male groups). Groups 1-3 in each gender received GABA (10, 50, 100μmol/kg/day) for 3 days, and then were subjected to renal IRI .Group 4 in each gender was subjected to renal IRI alone, and group 5 was subjected to surgical operation without renal IRI.24 hr after I/R injury, blood sample was obtained, and the animal were sacrificed for pathology investigation.

Results: Renal IRI alone increased the serum blood urea nitrogen levels (BUN) and creatinine (Cr), and kidney damage in both male and female rats significantly ($P<0.05$), however all doses of GABA decreased the serum BUN and Cr levels and tissue damage when compared with control group.

Conclusion: From the results of this study it seems that GABA administration in hyperglycemic rats could decrease renal injury after an ischemia/reperfusion.

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Introduction:

Ischemia/reperfusion injury (IRI) is an inevitable consequence of the procedure of kidney transplantation and has a negative impact on survival. The initial non immune injury leads to the activation of an innate immune response causing variable degrees of tissue damage (1-3). Acute kidney injury is a frequent clinical syndrome with high morbidity and mortality (1,4,5). The exact mechanisms underlying the IRI are not fully understood, however several factors are involved in the pathogenesis (6). The direct renal nerve stimulation produces frequency-dependent renal hemodynamic alteration which increases norepinephrine overflow into the renal vein (7).

The increased norepinephrine and renal sympathetic nerve activity were markedly enhanced on IRI in rats (8,9). γ-Aminobutyric acid (GABA) is well known inhibitory neurotransmitter in central

nervous system (10-14). The central administration of GABA or GABA agonist decreases blood pressure by inhibiting the sympathetic tone, thereby suggesting that GABA plays an important role in the inhibitory control of blood pressure by central nervous system (10,15,16). On the other hand, it has been reported that GABA inhibits vascular contraction induced by norepinephrine released by electrical nerve stimulation in the isolated rabbit ear artery, rat kidney and mesenteric arterial bed (8,17,18). These findings indicate that GABA inhibits not only central but also peripheral sympathetic neurotransmitters (19-21). GABA prevents diabetic hyperglycemia (22,23), and it is also known as an antioxidant which can be helpful in destroying free radicals (11,19,24). It is showed that GABA treatments enhanced the activities of antioxidant enzyme (25).

Diabetes is a metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (26-29). The chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Hyperglycemia is the onset of diabetes mellitus (DM) (27,30), and it is diagnosed when the blood sugar is more than 126 mg/dl (27,31,32). Recently studies have shown that sex hormones improve the long-term function of the renal allograft (1-3). On the other hand some document evidence suggests that gender and/or sexual steroids may play a role in the recovery from ischemic injury in non-renal organs such as heart and brain (33,34). But the course of post ischemic renal failure has not been compared between males and females in hyperglycemic model. So the aim of this study is to investigate the renoprotective effects of GABA on renal IRI in the female and male hyperglycemic model rats.

Methods:

Animals

In the experimental study adult male (184.4±4.4 g) and female (173.3±2.8 g) Wistar rats (Animal Centre, Isfahan University of Medical Sciences, Isfahan, Iran) were used in this study.

The animals were handled in accordance with the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" (http://www.nap.edu/readingroom/books/labrats/). Animals were housed at a room temperature of 23–25°C and 12 h light/12 h dark cycle with free access to water and rat chow. The animal experimental method was approved in advance by Hormozgan Ethic Committee.

Experimental protocol

Animals received a single dose of streptozotocin (STZ, 60 mg/kg i.p.). Six days later, the blood level of glucose was measured using glucometer (ACCU-CHEK ACTIVE, GC model Germany) and the rats with blood levels of glucose above 250 mg/dl were included in the study as diabetic rats. The 60 diabetic female and male rats were categorized into 10 groups (6 rats in each group). Male and female groups were assigned as 1-5 and 6-10, respectively.

Groups 1-3 in each gender (called GABA 10, 50, 100): Diabetic rats received GABA (10, 50, 100umol/kg ip) for three days and then subjected to renal IRI.

Group 4 in each gender (called ischemia): Diabetic rats received normal saline (0.5 ml ip) for three days continuously, then subjected to renal IRI.

Group 5 in each gender (called sham): Diabetic rats received normal saline (0.5 ml ip) for 3days continuously and then they were subjected to renal IRI.

One day (24 hr) post reperfusion blood sample was obtained, and they were sacrificed, and the kidney was removed rapidly for pathology investigation.

Renal IRI

The rats were anesthetized by injecting chloral hydrate (450mg/kg). The kidney IRI procedure was applied as described before [1]; briefly two small incisions were made on the skin of the animal flunk, and the fascia was gently removed to appear the kidneys. The both kidneys'renal arteries and veins were occluded with a non-traumatic clamp for 45 min. At the end of the ischemic period, the clamps were released to allow reperfusion. The animals were recovered after surgery for the following steps of an experiment.

Measurements

The serum level of Cr and BUN were measured using diagnostic kits (Pars Azmoon Co., Tehran, Iran) and Autoanalyzer device (Technicon RA 1000, Ireland). The amounts of serum and urine nitrite were measured using assay kit (Promega Corporation, Madison, WI, USA). The renal and serum amounts of malondialdehyde (MDA) were measured by manual method using trichloroacetic acid and thiobarbituric acid.

Histopathology procedures

The left kidney was fixed in 10% neutral formalin solution, after that it embedded in paraffin wax for hematoxylin and eosin staining to examine the tubular damage. A pathologist who was completely blind to the study protocol and administered medications evaluated the damage. Kidney tissue damage score (KTDS) was graded as follows: no damage (0), mild (1; unicellular, patchy isolated damage), moderate (2; damage less than25%), severe (3; damage between 25 and 50%), and very severe (4; morethan 50% damage).

Statistical analysis

Data were expressed as mean ± standard error of mean. One-way ANOVA followed by the least significant difference test (LSD) and Kruskal–Wallis/Mann–Whitney U-tests were applied for quantitative and qualitative data respectively. $P<0.05$ was considered as significant.

Results:

The serum levels of BUN and Cr and KTDS showed a significant increase in renal IRI alone groups (group 4 in each gender) when compared with sham operated groups ($P<0.05$) (Figure 1,2).

However, all doses of GABA decreased the serum level of BUN and Cr and tissue damage when compared with control group significantly ($P<0.05$). In addition, no significant differences were observed between GABA groups regarding to BUN and Cr levels (Figure 1,2).

Legenth

Fig.1 The serum levels of blood urea nitrogen (BUN), creatinine (Cr), malondialdehyde (SMDA), kidney tissue MDA (KMDA), kidney tissue damage score (KTDS), and kidney weight (KW) in male experimental groups (1-3 GABA 10, 50, 100μmol/kg/day respectively for 3 days, and then were subjected to renal IRI. Group 4 was subjected to renal IRI alone, and group 5 was subjected to surgical operation without renal IRI). The star indicates significant differences from others groups ($P<0.05$). See the text for group number.

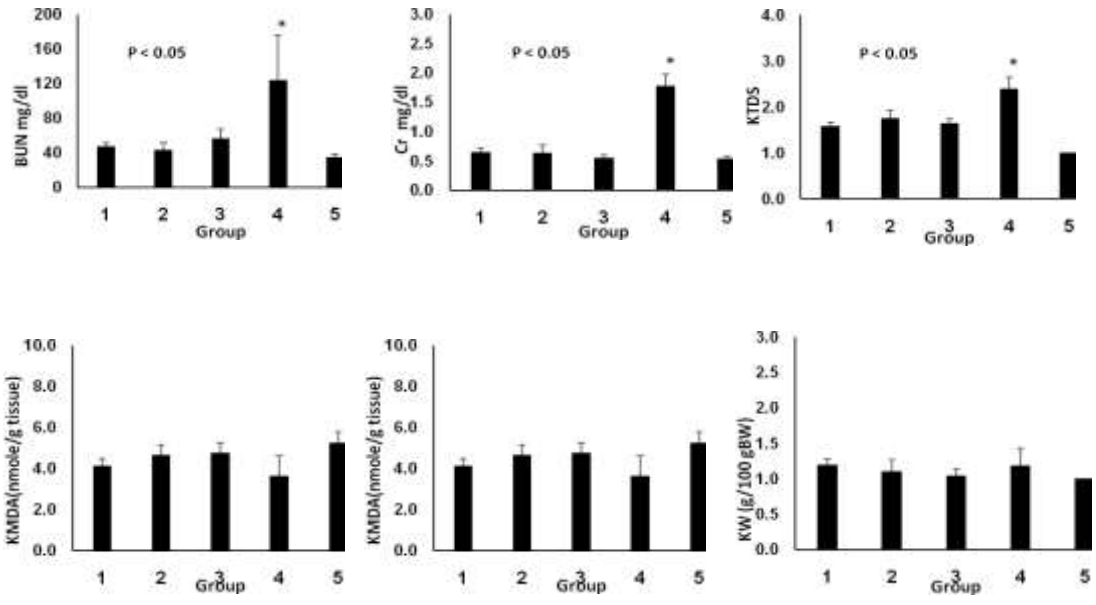

Figure 1. Male

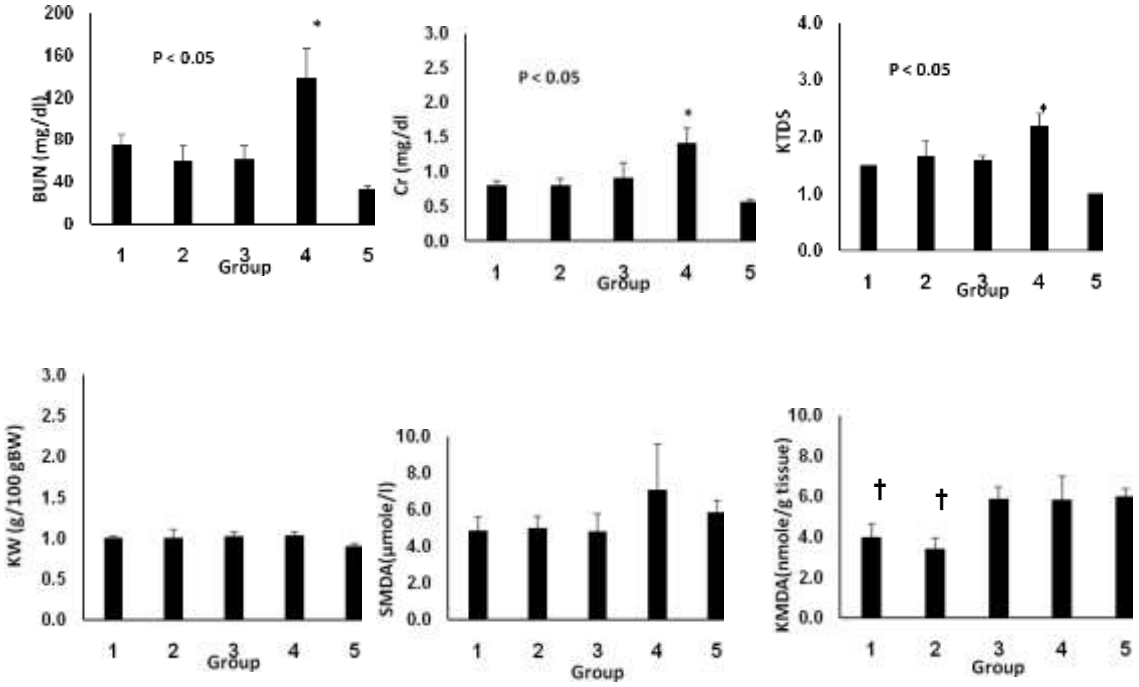

Figure 2. Female

Fig.2 The serum levels of blood urea nitrogen (BUN), creatinine (Cr), malondialdehyde (SMDA), kidney tissue MDA (KMDA), kidney tissue damage score (KTDS), and kidney weight (KW) in female experimental groups (1-3 received GABA 10, 50, 100μmol/kg/day respectively for 3 days, and then were subjected to renal IRI. Group 4 was subjected to renal IRI alone, and group 5 was subjected to surgical operation without renal IRI). The star indicates significant differences from others groups, and † indicates significant differences from groups 3-5 ($P<0.05$). See the text for group number.

Despite of former data, kidney weight and serum MDA levels didn't fluctuate magnificently in all GABA groups when compared with control group, but kidney tissue level of MDA in groups 1 & 2 in female rats were significantly different from others three groups ($P<0.05$). But there was no significant difference between the two genders.

Conclusion:

The main objective of this study was to investigate the renoprotective effects of GABA on renal IRI in hyperglycemic male and female rats. All dose of GABA protect the kidney against IRI dose independently.

Previous studies in nondiabetic rats, indicated that renal IRI caused kidney damage by increasing BUN and Cr levels in serum and kidney tissue damage (8,9) as we found here in hyperglycemic rats, and hyperglaycemia itself did not protect the kidney against IRI. On the contrary, it has shown that hyperglycemia has protective effects on kidney damage induced by cisplatin (35). Therefore the protective role of hyperglycemia is not general for all types of kidney damage. On the other hand, GABA has been shown as an antioxidant, blood sugar reducing and vasorelaxant agent (20,24,36-38). The renal tissues are documented to be involved in GABA synthesis and the kidneys are known to possess various subtypes of GABA receptors (39,40). It seems that GABA could be involved in regulating renal function. Kobuchi et al findings indicate that the suppressive effects of GABA against IRI were abolished by blockade of GABAB receptors, but not by blockade of GABA A receptors (11). In our previous findings we support the hypothesis that GABA B receptor express in abnormal condition such as STZ diabetic vessels and the GABA relaxatory effect is mediated by both GABA A and B receptors, but this effect

just mediated by GABA A receptor in normal vessels (41,42). GABA also can decrease the free radicals by reducing oxidative stress and is able to reduce the blood sugar by regenerating islet beta cells in pancreas and stimulate Glucagon-Like-Peptide-1 (GLP1) which can decrease hyperglycemia by insulin release stimulation (43-47). Although the reduction of serum glucose level by GABA may vanish the protective role of hyperglycemia, but, the antioxidant property of GABA may protect the kidney damage against IRI (47). Because some study believed that mitochondrial reactive oxygen species (ROS) production during IRI plays an important role in kidney damage (48). On the other hand reperfusion-induced local inflammatory response in kidney tissue has been well documented previously in a number of studies (49). It has been shown that TNF-α and other cytokines play an important role in early I/R injury (49). Our previous study showed that GABA is able to reduce TNF-α and other cytokine in diabetic mice (20).

Other parameters such as kidney tissue and serum levels of MDA were not influenced by GABA, but low and medium doses of GABA decrease kidney level of MDA in female. Such finding was not observed by high dose of GABA possibly related to reverse action of antioxidant when use with high doses. Previous study (49) has been suggested to be closely related to lipid peroxidation, as a free radical generating system, and I/R induced tissue damage, and MDA is a good indicator of the rate of lipid peroxidation.

Although the studies showed that gender influences normal renal hemodynamics and some researcher found that sex female hormone increases afferent and efferent arteriolar resistance and then decrease whole-kidney and single nephron GFR and blood flow (1-3), however we have not seen any significant differences between plasma and kidney parameters in male and female rats. But due to financial limitation the mechanism of GABA action was not investigated to make the better conclusion.

It is concluded that the administrations of different doses of GABA are able to decrease kidney injury and damage in renal IRI due to its antioxidant effect. Glucose reduction effect of GABA and its antioxidant effect may have some advantage to use in renal IRI in diabetic model.

Conflict of interest:

The authors declare no conflict of interest.

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اثرات محافظتی گابا بر روی صدمات ناشی از ایسکمی – ری پرفیوژن کلیوی در رتهای نر وماده هیپرگلایسمی

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مجله پزشکی هرمزگان سال بیست و یکم شماره اول ۹۶ صفحات ۹-۱

چکیده

مقدمه: *آسیب حاد کلیوی یکی از مشکلات پیچیده بیماران دیابتی است. علت اصلی آسیب حاد کلیوی ایسکمی – ری پرفیوژن است. این مطالعه طراحی شده است تا اثرات محافظتی گابا را بر روی ایسکمی-ریپرفیوژن(IRI) در رتهای نر و ماده هیپرگلایسمی بررسی نماید.*

روش کار: *۶۰ عدد رت نر وبیستار و ماده که با STZ دیابتی شده بودند به ۱۰ گروه تقسیم شدند. گروه ۱-۳ در هردو جنس گابا با دوزهای (10, 50, 100µmol/kg/day) برای سه روز دریافت نمودند و سپس IRI در آنها القا شد. گروه چهار در هر دو جنس فقط مورد IRI قرار گرفتند. گروه پنج در هر دو جنس فقط جراحی شدند بدون القای IRI ۲۴ ساعت بعد از ایسکمی- ری پرفیوژن از حیوانات خون گیری صورت گرفت و پس از آن حیوانات کشته شدند.*

نتایج: *IRI به تنهایی سبب افزایش معنی‌دار $P<0.05$ اوره ازت خون (BUN)، کراتنین (Cr) و آسیب حاد بافت کلیه در هر دو جنس شد. اما تجویز تمام دوزهای گابا سبب کاهش معنی‌دار BUN, Cr و آسیب بافت کلیه در مقایسه با گروه کنترل در هر دو جنس شد.*

نتیجه‌گیری: *از نتایج این مطالعه این طور به نظر می‌رسد که تجویز گابا توانسته است صدمات ناشی از ایسکمی ری – پرفیوژن کلیوی را در هر دو جنس کاهش دهد.*

کلیدواژه‌ها: *ایسکمی، ری پرفیوژن، دیابت، گابا، رت*

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