1- Ischaemia-reperfusion injury in renal transplantation: the role of nitric oxide in an experimental rat model

OBJECTIVE
To investigate the role of nitric oxide (NO) in ischaemia-reperfusion (I/R) injury in a renal transplant rat model, as I/R injury is a common consequence of renal transplantation and NO has many protective properties that might protect the kidney after I/R injury.

MATERIALS AND METHODS
In all, 30 male Sprague-Dawley rats weighing 350–400 g and aged 4–6 months underwent renal transplantation and received FK506 (an immunosuppressant) to overcome early acute rejection episodes. The rats were divided randomly into three groups (10 rats each): Group I, treated with FK506 (2 mg/kg body weight [bw], once daily), served as the control group; Group II, treated with FK506 2 mg/kg bw and L-arginine 300 mg/kg bw; and Group III, treated with FK506 (2 mg/kg bw) and, n-omega-nitro-l-arginine methyl ester (L-NAME; 50 mg/kg bw). Urine and blood samples were taken at 0 (before operation), 2, 7, and 14 days after transplantation for estimation of urine sodium, creatinine, fractional excretion of sodium, serum creatinine, sodium, and blood urea nitrogen (BUN). Kidney specimens were taken for histological examination by light microscopy.

RESULTS
Serum creatinine and BUN levels significantly decreased in the L-arginine-treated group (both P < 0.001) while they were significantly increased in the L-NAME-treated group (P < 0.005 and P < 0.001, respectively) compared with the control group at all time intervals. Light microscopic examination of the renal biopsies in the control group showed acute tubular necrosis, which was minimal in kidneys transplanted and treated with L-arginine and more markedly with L-NAME.

CONCLUSION
I/R injury impaired graft function during the first week after transplantation. Injection of L-arginine before ischaemia antagonized graft deterioration and improved morphological appearance.

2- Effects of combined erythropoietin and epidermal growth factor on renal ischaemia/reperfusion injury: a randomized experimental controlled study

OBJECTIVE
To investigate effects of combination of erythropoietin (EPO) and epidermal growth factor (EGF) on renal ischaemia and on reactive oxygen species in a rat model.

MATERIALS AND METHODS
In all, 90 male Sprague-Dawley rats were allocated into five groups of 18, designated: Sham; treated with right nephrectomy only; Control, subjected to left renal ischaemia for 45 min with no treatment; EPO-treated, as the control but with EPO pretreatment; EGF-treated, as the control but with EGF pretreatment; EPO + EGF-treated, as the control but with EPO and EGF pretreatment. Renal function, histopathology and malondialdehyde (MDA), superoxide dismutase (SOD) and reduced glutathione (GSH) levels in kidneys were assessed at 1, 2 and 7 days after ischaemia.

RESULTS
All rats except the controls had a significant improvement in serum creatinine, creatinine clearance and fractional excretion of Na+; all three were significantly better in EPO + EGF group than in all other groups. Histopathological examination showed marked structural damage in control rats. The tubular damage was least in the EPO + EGF group. The control group had a significant increase in MDA level and a significant decrease in SOD and GSH, while the EPO + EGF group had a marked significant reduction in MDA and increase in GSH and SOD.

CONCLUSION

The protection against ischaemia/reperfusion injury might be maximal when EPO and EGF are administered concomitantly, and their protective effect might be partly due to their antioxidant effects.

3-

Recoverability of Renal Functions after Relief of Partial Ureteral Obstruction of Solitary Kidney: Impact of Ferulic Acid

Objectives: To evaluate the effect of Ferulic acid (FA) on the recovery of renal function and renal damage after relief of partial ureteral obstruction (PUO) of a solitary kidney.

Methods: thirty-two male mongrel dogs were classified into three groups: sham (8), control (12) and study (12). Right nephrectomy was done and dogs in the study and control groups were subjected to 4 weeks of PUO. Serum creatinine, creatinine clearance (CrCl), and renographic clearance (RC) were measured at baseline, 4 weeks of obstruction and 8 weeks after relief of obstruction. Markers of lipid peroxidation (malondialdehyde MDA), superoxide dismutase (SOD), and reduced glutathione (GSH), and immunostaining of markers of apoptosis (caspase 3 and Bcl2), cell proliferation (ki67) and interstitial fibrosis in the kidney were evaluated at the end of experiment.

Results: FA enhanced the recovery of serum creatinine, CrCl and RC by an extra 22%, 26%, and 33.7% of the basal values at 8 weeks, after relief of 4 weeks obstruction, respectively. Also, FA caused significant decrease in MDA, and significant increase in GSH and SOD. Moreover, FA significantly reduced the interstitial fibrosis, and caspase 3 expression, and significantly increased the expression of Bcl2 and ki67 in kidney tissues at 8th week after relief of obstruction. Conclusion: FA enhances the recoverability of renal function and minimizes the renal damage through reduction of oxidative stress, tubular apoptosis and the interstitial fibrosis in the solitary kidney after relief of PUO.

4-

Renal ischaemia/reperfusion injury: possible role of aquaporins

Renal ischaemia/reperfusion (I/R) injury is a common problem that occurs when blood flow is interrupted to the kidney in case of kidney transplantation, aortic cross-clamping and shock with subsequent resuscitation. Renal I/R injury is a complex conditions which includes the onset of an inflammatory process, which is associated with impairment of concentrating ability of the kidney and impairment of solute transport. Characteristically, renal I/R injury is associated with marked reduction in the protein expression of renal aquaporins (AQPs) mainly (AQP1, AQP2 and AQP3), and solute transporters were observed in this condition and could account for the impaired urinary concentration that observed in this condition. Recently, many agents were tested for a possible protective effect against this insult such as erythropoietin.
(EPO), a-melanocyte-stimulating hormone (a-MSH) and a-lipoic acid which were proved to prevent downregulation of AQPs and solute transporters. The aim of this short review is to outline the potential pathophysiological role of AQPs in renal I/R injury and to put a spotlight on the modulation of renal functions impairment in renal ischaemia by new drugs that prevent downregulation of AQPs.

5-

**Myocardial and metabolic dysfunction in type 2 diabetic rats: impact of ghrelin**

Abstract

Diabetes mellitus (DM) is commonly associated with metabolic and cardiac dysfunctions. The aim of this study was to examine the effect of ghrelin on metabolic and cardiac dysfunctions in a type-2 diabetes mellitus (T2DM) rat model. For this, 48 male adult Sprague-Dawley rats were divided equally into 4 groups: Group I, fed normal chow, served as normal control group; Groups II-IV, were fed a high-fat diet for 2 weeks followed by injection of streptozotocin (STZ) (35 mg/kg body mass) to create a model of T2DM; Group II, were not treated; Group III, were treated with the vehicle (saline); Group IV, were treated with ghrelin (40 \( \mu \)g/kg body mass) twice daily for 10 days. The untreated diabetic rats showed a significant increase in serum fasting blood glucose, insulin homeostasis model assessment (HOMA) index, triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), total serum cholesterol (TC), and body mass, with a decrease in high-density lipoprotein cholesterol (HDL-C) (p < 0.05). Hearts isolated from diabetic rats showed a significant increase in myocardial fat content, a significant decrease in GLUT4, and an increase in acyl-CoA oxidase enzyme mRNA (p < 0.05). Ghrelin administration for 10 days caused a significant improvement in lipid profile, HOMA index, and body mass, and significantly corrected the myocardial mass, significantly reduced the fat content of the myocardium, significantly increased GLUT4, and decreased acyl CoA oxidase mRNA (p < 0.05). Thus, ghrelin improves both the metabolic functions and the disturbed energy metabolism in the cardiac muscle of obese diabetic rats.

6-

**Influence of age on pain sensitivity in response to paw pressure and formalin injection in rats: a role of nitric oxide**

Abstract

The effect of age on pain response to paw pressure and intraplantar formalin injection in rats is elucidated. Pain responses evoked by mechanical pressure on hind paw and intraplantar injection of formaldehyde (5%) into the hind paw were evaluated in groups of adult, young and aged male Sprague Dawley rats, after intraperitoneal (i.p.) or intracerebroventricular (i.c.v.) injection of L-arginine or NG-nitro-L-arginine methyl ester (L-NAME). Nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase staining was done in the two groups. The results show that pain response was reduced in the aged rats and enhanced pain response to paw pressure in aged rats only. L-arginine
(i.c.v.) had no effect on pain response to paw pressure in the two groups but enhanced biphasic pain response to formalin. L-NAME (i.p. and i.c.v.) suppressed pain response to paw pressure in the two groups. L-NAME (i.c.v.) suppressed pain response to formalin during the acute phase and enhanced it during the late phase. NADPH-diaphorase activity was significantly greater in young rats. In conclusion, pain response is blunted in the aged rats. NO might be involved in mechanical nociception in aged rats and in formalin-induced nociception in both groups. NO blockade has an antinociceptive effect on pain response. Central NO has dual role in pain response evoked by formalin.

7-

**Effect of chronic excess iodine intake on thyroid function and oxidative stress in hypothyroid rats.**

Abstract

Our objective was to investigate the effects of chronic excess iodine intake on thyroid functions and thyroid oxidative stress state in hypothyroid rats. Sixty rats were divided into euthyroid and hypothyroid (thiocyanate-induced) groups with or without administration of excess iodine (3000 or 6000 \( \mu \)g/L) for 8 weeks. Serum thyroxine (T(4)), triiodothyronine (T(3)), thyroid-stimulating hormone (TSH), thyroid antioxidants (catalase, superoxide dismutase enzymes, and total antioxidants), and lipid peroxide (malondialdehyde; MDA) were measured. Reverse transcription - PCR gene expression for thyroidal Na(+)I(-) symporter (NIS), D1 deiodinase, and thyroid peroxidase (TPO) were performed. Thiocyanate significantly decreased thyroid hormones (T(3), T(4)), increased lipid peroxides and antioxidants, and increased gene expression of NIS, D1 deiodinase, and TPO. Excess iodine intake in hypothyroid rats increased T3 and T4. Also, high iodine intake by hypothyroid rats significantly decreased NIS, D1 deiodinase, and TPO genes expression. Excess iodine significantly increased MDA and antioxidants in euthyroid and hypothyroid rats. In conclusion, thiocyanate-hypothyroidism increases gene expression of NIS, TPO, and TPO and induces oxidative stress. High iodine intake decreases NIS and D1 deiodinase gene expression in hypothyroid rats. Moreover, excess iodine increase thyroid hormones, lipid peroxides, and antioxidants in hypothyroid rats.

8-

**Systemic and renal haemodynamic changes in renal schema/reperfusion injury: impact of erythropoietin**

Abstract

The objective of this study was to investigate the effects of erythropoietin (EPO) on systemic and renal hemodynamics in a rat model of renal ischemic/reperfusion (I/R) injury. We used 30 male Sprague-Dawley rats distributed among the following 3 groups (10 rats per group): (i) the sham-operated group, (ii) the control group (I/R injury only), and (iii) the EPO-treated group (I/R injury with 1500\( \text{U} \cdot \text{kg}^{-1} \cdot \text{day}^{-1} \) on day 0 and 1 day 2 and 4 after ischemia). Renal function,
arterial blood pressure (ABP), renal plasma flow (RPF), renal blood flow (RBF), and renal vascular resistance (RVR) were measured on days 1, 2, and 7 after ischemia. The expression of endothelial NO synthase (eNOS) and histopathology of kidney were evaluated on day 7. The contractility of aortic strips was recorded from the different groups. The results show that renal function and histopathology were significantly improved after treatment with EPO. Compared with the control group, the EPO-treated group showed a significant increase in RPF, RBF, haematocrit, ABP, eNOS expression, and a decrease in RVR (p < 0.05). The response of aortic strips to the relaxant effect of acetylcholine was improved in the EPO-treated group. In conclusion, treatment with EPO improves renal function and renal haemodynamics in renal I/R injury, and causes significant rise of ABP and haematocrit value.

Protection against renal ischaemia/reperfusion injury: A comparative experimental study of the effect of ischaemic preconditioning vs. postconditioning

Objective

To compare the effect of ischaemic preconditioning (Ipre) vs. ischaemic postconditioning (Ipost) on renal ischaemia/reperfusion (I/R) injury in rats.

Materials and methods

In all, 120 male Sprague–Dawley rats were classified into four groups of 30 rats each, designated sham, control, Ipre and Ipost. Renal function, including serum creatinine, blood urea nitrogen (BUN), creatinine clearance (CrCl), fractional Na excretion (FENa) and renal histopathology were measured at 2, 24 and 48 h after ischaemia. Markers of lipid peroxidation (malondialdehyde, MDA), superoxide dismutase (SOD) and reduced glutathione (GSH) were measured in kidney tissues during the same intervals.

Results

Ipre caused a significant improvement in renal function, as indicated by a significant decrease in serum creatinine, BUN and FENa, with a significant increase in CrCl. However, Ipost caused no significant improvement in renal function. Morphologically Ipre caused a marked significant improvement in the renal tubular damage score compared to Ipost. Also, Ipre caused a significant decrease in MDA, and significant increase in GSH and SOD when compared to Ipost.

Conclusion

Ipre is more potent than Ipost for improving the renal injury induced by I/R. Ipre caused a marked improvement in renal function and morphology, while Ipost caused a minimal improvement in morphology only. Moreover, Ipre caused a marked and significant reduction in oxidative stress in kidney tissues, while Ipost caused a minimal reduction.