Research Journal of Pharmacology 8 (2): 6-13, 2014
ISSN: 1815-9362

The Protective Effect of Dexamethasone, Aspirin and Bromocriptine on Hepatic Ischemia/Reperfusion Injury in Rats

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Abstract: This study aimed to investigate the protective effects of dexamethasone, aspirin and bromocriptine on hepatic ischemia/reperfusion-induced liver injury. About 60 male Wistar Albino rats were randomly assigned to 6 groups of 10 rats each. Group 1 served as negative control, group 2 served as hepatic I/R control injury. Rats in groups 3-6 received N-acetylcysteine (standard, 100 mg/kg/day, i.p.), dexamethasone (5 mg/kg/day, i.p.), aspirin (10 mg/kg/day, i.p.) and bromocriptine (10 mg/kg/day, i.p.), respectively for 3 consecutive days prior to ischemia. All animals were fasted for 12 h, anaesthetized with thiopental and underwent midline laparotomy. The portal vein, hepatic artery and bile duct (portal triad) were clamped by mini-artery clamp for 30 min followed by reperfusion for 30 min. At the end of the experiment, blood samples were withdrawn for estimation of serum Alanine Transaminase (ALT) and Aspartate Transaminase (AST) activities in addition to assessment of hepatic Thiobarbituric Acid Reactive Substances (TBARS), Glutathione (GSH), Myeloperoxidase (MPO) and total nitrate/nitrite (NO_x) production, as well as histopathological examination. Dexamethasone, aspirin and bromocriptine significantly ameliorated hepatic I/R injury as evidenced by significant reduction in serum ALT and AST enzyme activities. Dexamethasone, aspirin and bromocriptine markedly reduced hepatic oxidative stress biomarkers as compared to control I/R injury. The inflammatory mediators MPO and NO_x levels in liver were also significantly reduced after treatment with dexamethasone, aspirin and bromocriptine. In accordance, a marked improvement of histopathological findings was observed with any of the 3 treatments. Dexamethasone, = aspirin and bromocriptine seem to offer protection against hepatic ischemia/reperfusion-induced liver injury and are promising for further clinical trials.

Key words: Histopathological, bio markers, hepatic oxidatine, bromocriptine, treatment

INTRODUCTION

Ischemia/Reperfusion (I/R) injury occurs during the procedure of liver transplantation, liver resection, trauma and other surgical procedures when the liver is transiently deprived of oxygen and subsequently re-oxygenated (Fondevila *et al*., 2003; Selzner *et al*., 2003; Vardanian *et al*., 2008). Injury to the liver caused by I/R has been shown associated with increased rate of acute liver failure/graft rejection and chronic liver dysfunction after liver transplantation (Fang *et al*., 2013).

The mechanism of liver damage after I/R has been studied extensively. The signaling events contributing to cellular and tissue damage are diverse and complex and consist of complex interactions of multiple inflammatory pathways (Montalvo-Jave *et al*., 2008; Vardanian *et al*., 2008), as well as production of reactive oxygen species (Wanner *et al*., 1996). Proinflammatory cytokines, Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-1β are known to increase in serum and liver tissue on reperfusion and have a pivotal role in the pathophysiology of hepatic I/R injury (Tsung *et al*., 2005; Liu *et al*., 2011).

Inflammation plays an important mechanistic role in the progression of hepatic I/R injury (Batkai *et al*., 2007). Structural alterations during ischemia stimulate cytotoxic immune response (Adachi *et al*., 2006). On reperfusion, Tumor Necrosis Factor-α (TNF-α), induced by activated endothelium, acts as a continuous stimulator for neutrophil infiltration into the liver (Jaeschke, 2006). Production TNF-α and other cytokines, also stimulates the induction of inducible Nitric Oxide Synthase (iNOS) enzyme in hepatocytes, followed by massive production of nitric oxide (Yanagida *et al*., 2006). Excessive NO production by iNOS is known to potentiate the hepatic oxidative injury in I/R (Chen *et al*., 2003), as NO may combine with superoxide radical to form peryoxynitrite, a substance extremely toxic to cells (Beckman *et al*., 1990).

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NO also inhibits the Kreb's cycle enzymes of mitochondria in hepatocytes, resulting in further decrease of hepatic ATP contents (Stadler *et al*., 1991; Tu *et al*., 2003).

Dexamethasone possesses pleiotropic pharmacological activities which include anti-inflammation (its most powerful effect), anti-virus, antishock and anti-immunization can inhibit the inflammatory reactions caused by manifold factors and has been extensively applied to the treatment of severe infections (Zhang *et al*., 2007). Steroids in general have pronounced anti-inflammatory and immunosuppressive properties decreasing edema and collagen deposition, inhibiting scarring and arresting migration of infiltrating monocytes and lymphocytes. They have a broad range of specific immune response mediated by T and B cells, as well as suppressive effect on the effector function of monocytes, macrophages and neutrophils. Once bound to its ligand, the glucocorticoid receptor complex is translocated to the nucleus where it binds to promoter regions of genes susceptible to steroid regulation. Glucocorticoids inhibit synthesis of many proinflammatory cytokines by inhibiting the transcription factor for Nuclear Factor Kappa B (NF-κB) and Activator Protein-1 (AP-1) (Muratore *et al*., 2009).

Aspirin (Acetylsalicylic Acid, ASA), a Non-Steroidal Anti-Inflammatory Drug (NSAID) is used widely to relieve pain, fever and peripheral inflammation (Basselin *et al*., 2011). Aspirin irreversibly inhibits Cyclooxygenase (COX)-1 which converts arachidonic acid to prostaglandin endoperoxides and thus, reduces Prostaglandin (PG) and Thromboxane (TX) formation (Vane, 1971). Aspirin also acetylates COX-2 (Meade *et al*., 1993) which converts arachidonic acid to 15 (R)-Hydroxyeicosatetraenoic acid (HETE) which then can be metabolized by 5-Lipoxygenase (5-LOX) to 15-epimeric Lipoxin (LX) A4 and B4 (15-epi-LX) in leukocytes and endothelial cells (Claria and Serhan, 1995). Lipoxins generated by the actions of 5-and 12-LOX or of 15-and 5-LOX and 15-epi-LX play key roles in resolution of the inflammatory reaction (Chiang *et al*., 2005; Serhan, 2005).

Bromocriptine (BRC), a Dopamine (DA) D2 receptor agonist and mild D1 receptor antagonist is widely used in the treatment of Parkinson's disease, since 1974 and in a broad spectrum of psychiatric disorders (Schapira, 2003). It reduces the formation of oxygen radicals in the course of normal metabolism of levodopa and DA (Yoshikawa *et al*., 1994). Recent observations suggest that bromocriptine is an antioxidant that inhibits free radical formation and acts as a strong free radical scavenger *in vitro* and *in vivo* (Lim *et al*., 2008). Bromocriptine protects cells by enhanced intrinsic defense mechanism against oxidative stress (Xing *et al*., 2005).

The present study was performed to illucidate the possible hepatoprotective potentials of dexamethasone, aspirin and bromocriptine on hepatic ischemia reperfusion injury in rats. N-Acetylcysteine (NAC) was chosen as the reference standard in the present study owing to its well studied and documented hepatoprotective properties.

To achieve this goal, several parameters were measured including, include serum Alanine Transaminase (ALT) and Aspartate Transaminase (AST) activities to elucidate hepatocellular damage; hepatic contents of Thiobarbituric Acid Reactive Substances (TBARS) and reduced Glutathione (GSH) to estimate oxidative stress; hepatic Myeloperoxidase (MPO) and total nitrate/nitrite (NO_X) as a measure of inflammation in addition to a histopathological study.

MATERIALS AND METHODS

Animals and treatments: Adult male Albino rats of body weights ranging from 210-230 g were used. They were housed in the animal room in Pharmacology Department, Faculty of Pharmacy under conventional laboratory conditions on 12 h light/dark cycle and constant temperature (22±1°C). Throughout the study food and water were supplied *ad libitum*. Exactly 12 h before hepatic Ischemia/Reperfusion (I/R) operation animals were fasted (Xu *et al*., 2006). During fasting, animals were allowed free access to water and individually kept in separate cages with bottom stainless steel mesh to avoid coprophagy (Sibilia *et al*., 2003).

All experimental procedures were conducted in accordance with ethical procedures and policies approved by the Ethics Committee of Faculty of Pharmacy, Beni Suef University.

Experimental design: After the accommodation period of 1 week rats were divided into 6 groups (n = 10 rats in each group) as follows:

Group 1: Normal control; this group did not receive any medication and underwent sham operation
Group 2: Hepatic I/R control injury; this group did not receive any medication and underwent I/R operation

The groups 3 through 6 were treated with standard or test drugs for 3 consecutive days prior to hepatic I/R injury in the indicated doses as follows:

Group 3: N-acetylcysteine (100 mg/kg/day, i.p.)
Group 4: Dexmethasone (5 mg/kg/day, i.p.)
Group 5: Aspirin (10 mg/kg/day, i.p.)
Group 6: Bromocriptine (10 mg/kg/day, i.p.)

Standard and test drugs were suspended in 1% tween 80 and administered on a daily basis for 3 days with the last dose administered 1 h prior to ischemia. Blood and liver samples were rapidly collected after reperfusion.

Induction of hepatic I/R injury: The I/R Model was performed, according to the method described by Colletti *et al.* (1990) with a slight modification. Rats were fasted for 12 h before the operation, anaesthesized with thiopental sodium, 70 mg kg^{-1}, i.p. and underwent midline laparotomy. The portal vein, hepatic artery, bile duct and caudate hepatic lobe were freed by blunt dissection with the hepatoduodenal ligament separated. The portal vein, hepatic artery and bile duct (portal triad) were clamped by mini-artery clamp for the indicated time (30 min) (Suzuki *et al*., 1999; Inal *et al*., 2006); followed by reperfusion (30 min) (Aydemir *et al*., 2003; Boin Ide *et al*., 2006). With this technique, ischemia was induced in the median and left lateral lobes of the liver, accounting for 70% of the liver mass. Appropriate clamping was confirmed by visual inspection of the ischemic lobes. During the period of hepatic ischemia, the animal's abdomen was covered with plastic wrap to prevent dehydration.

Assessment of hepatic injury: Serum activities of ALT and AST enzymes were measured using test reagent kits based on the method of Reitman and Frankel (1957).

Hepatic TBARS content was assessed in the liver homogenate of median and left hepatic lobes according to the method described by Uchiyama and Mihara (1978).

Hepatic GSH content was assessed in the liver homogenate according to the method described by Sedlak and Lindsay (1968) after deproteinization with 12% trichloroacetic acid solution. Hepatic MPO activity was estimated, according to the method described by Harada *et al.* (1999). Total nitrate/nitrite production was assessed by the method described by Miranda *et al.* (2001).

Liver slides for histopathological study were prepared from the median lobes and stained with routine Hematoxylin and Eosin (H&E) staining, according to the method described by Bancroft and Stevens (1996).

Statistical analysis: Data were expressed as mean values±SEM. Comparison between the mean values of different groups was carried out by using one way Analysis of Variance (ANOVA), followed by Tukey-Kramer post hoc test for multiple comparisons. The $p<0.05$ were selected to indicate statistical significance between groups.

RESULTS

Serum ALT and AST: Serum ALT and AST were evaluated to reflect the liver function. Hepatic I/R injury significantly raised serum ALT and AST enzyme activities as compared to normal control group. Dexamethasone significantly ameliorated hepatic I/R injury, as indicated by significant reduction in serum ALT and AST enzyme activities as compared to hepatic I/R injury control. Values of serum ALT and AST were not significantly different from NAC treatment. Aspirin significantly suppressed serum ALT and AST enzyme activities, as compared to hepatic I/R injury control to values not significantly different from normal control values. Bromocriptine significantly reduced hepatic I/R injury, as evidenced by significant reduction in serum ALT and AST enzyme activities as compared to hepatic I/R injury control (Table 1).

Oxidative stress biomarkers: The effect of dexamethasone, aspirin and bromocriptine on oxidative stress biomarkers is summarized in Table 2.

Dexamethasone markedly reduced the oxidative stress biomarker MDA in serum as compared to control I/R injury. Aspirin markedly reduced the oxidative stress biomarker MDA in serum and significantly increased hepatic GSH content, as compared to control I/R injury. Bromocriptine significantly reduced the oxidative stress biomarker TBARS but did not significantly affect hepatic GSH content as compared to control I/R injury.

Liver MPO and NO_x: Dexamethasone, aspirin and bromocriptine significantly reduced live inflammatory mediators MPO and total nitrate/nitrites as compared to hepatic I/R control injury (Table 3).

Histopathologic findings: A photomicrograph of liver section of I/R control group showed that the structure

Table 1: Effects of dexamethasone, aspirin and bromocriptine on serum ALT and AST enzyme activities

		Hepatic I/R injury (n = 10)				
Variables	Sham control (n = 10)	Control	NAC	DEX	ASP	BROMO
Serum ALT activity (U L^{-1})	24.7±1.86	128.0±8.920*	47.6±2.96*@	66.0±5.60@	50.9±3.92*@	56.5±3.87*@
Serum AST activity (U L^{-1})	126.0±7.09	505.1±32.66*	234.8±17.16*@	263.3±16.59*@	216.3±18.09*@	294.5±13.46*@

Data was expressed as mean±SEM; Statistical analysis was performed using one-way ANOVA followed by Tukey-Kramer multiple comparisons test; *Significantly different from sham-operated control value at $p<0.05$; @Significantly different from hepatic I/R control value at $p<0.05$; NAC = N-Acetyl Cysteine; DEX = Dexamethasone; ASP = Aspirin; BROMO = Bromocriptine

Table 2: Effect of dexamethasone, aspirin and bromocriptine on liver MDA and GSH contents

		Hepatic I/R injury (n = 10)				
Variables	Sham control (n = 10)	Control	NAC	DEX	ASP	BROMO
Liver MDA (nmol g^{-1} wet tissue)	162.0±19.94	428.6±26.50*	146.2±12.34@	199.5±29.19@	192.3±11.18@	185.8±11.76@
Liver GSH (µmol g^{-1} wet tissue)	4.57±0.293	1.58±0.236*	4.49±0.303@	4.03±0.115@	3.94±0.220@	4.31±0.168@

Data was expressed as mean±SEM; Statistical analysis was performed using one-way ANOVA followed by Tukey-Kramer multiple comparisons test; *Significantly different from sham-operated control value at $p<0.05$; @Significantly different from hepatic I/R control value at $p<0.05$; NAC = N-Acetyl Cysteine; DEX = Dexamethasone; ASP = Aspirin; BROMO = Bromocriptine

Table 3: Effect of dexamethaone, aspirin and bromocriptine on liver MPO and total nitrate/nitrite

		Hepatic I/R injury (n = 10)				
Variables	Sham control (n = 10)	Control	NAC	DEX	ASP	BROMO
Liver MPO (U g^{-1} wet tissue)	1.40±0.102	3.94±0.176*	2.27±0.155*@	1.35±0.120@#	2.47±0.190*@	3.11±0.270*@#
Liver total nitrate/nitrite (µmol g^{-1} wet tissue)	6.53±0.414	11.54±0.704*	7.88±0.652@	6.17±0.538@	7.39±0.418@	8.26±0.657@

Data was expressed as mean±SEM; Statistical analysis was performed using one-way ANOVA followed by Student-Newman-Keuls multiple comparisons test; *Significantly different from sham-operated control value at $p<0.05$; @Significantly different from hepatic I/R control value at $p<0.05$; #Significantly different from standard treatment value at $p<0.05$; NAC = N-Acetyl Cysteine; DEX = Dexamethasone; ASP = Aspirin; BROMO = Bromocriptine

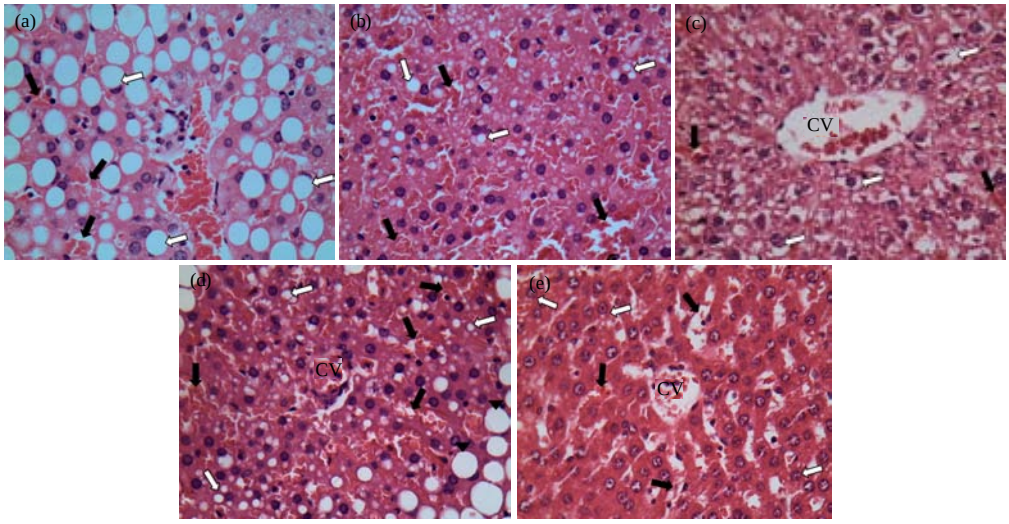

Fig. 1: a, b) A photomicrograph of liver section of I/R control group showing dilated and congested blood sinusoids (black arrows). Diffuse cytoplasmic lipid vacuolations of hepatocytes with signet ring appearance (white arrows); c) A photomicrograph of liver section of dexamethasone treated group showing dilated and congested Central Vein (CV) with slight congestion of blood sinusoids (black arrows). Hepatocytes show cytoplasmic degeneration (white arrow); d) A photomicrograph of liver section of aspirin treated group showing minimally congested Central Vein (CV) and blood sinusoids (black arrows). Hepatocytes seem to be normal but with tiny cytoplasmic vacuolations (white arrows); e) A photomicrograph of liver section of bromocriptine treated group showing slightly congested Central Vein (CV) and blood sinusoids (black arrows). Almost hepatocytes are normal except few with tiny cytoplasmic lipid vacuolations (white arrows)

of liver lobules were severly damaged. Dilated and congested blood sinusoids were observed in addition to diffused cytoplasmic lipid vacuolations of hepatocytes with signet ring appearance (Fig. 1a, b).

Nevertheless, the structure of liver hepatocytes was greatly restored after administration of dexamethsone (Fig.1c). A marked improvement of histopathological findings was observed in aspirin treated group. Hepatocytes seem to be normal but with tiny cytoplasmic vacuolations (Fig. 1d). The structure of hepatocytes was greatly improved after administration of bromocriptine. Almost hepatocytes are normal, except few with tiny cytoplasmic lipid vacuolations (Fig. 1e).

DISCUSSION

Results of the present study revealed that induction of hepatic I/R injury was associated with increased serum

ALT, AST activity, liver MDA , liver MPO and liver total nitrates/nitrites. In addition of decreased liver GSH. These results were further supported by histopathological examination which showed dilated and congested blood sinusoids and diffused cytoplasmic lipid vacuolations of hepatocytes with signet ring appearance. These findings are quite consistent with that of Cekin *et al.* (2013) who showed that identification of hepatic dysfunctions and cellular damage via increased levels for serum AST, ALT in the I/R groups indicates that I/R was successfully induced (Gomez-Amores *et al*., 2006).

Moreover, increased levels of liver MDA, MPO, total nitrates/nitrites and decreased level of liver GSH markers of oxidative liver damage could be attributed to lipid peroxidation which is thought to be one of the most important consequences of excessive free radical production that play a significant role in the mechanism of I/R injury by damaging structural and functional properties of cellular organelles (Masubuchi *et al*., 2005).

Mitochondrial proteins could be also the target for hepatic toxicity leading to the loss of energy production and cellular ion control (Yapar *et al*., 2007). Dysfunction is a energy-dependent metabolic pathways and transport mechanisms due to loss of mitochondrial respiration and subsequent reduction in ATP production was shown to be the leading factor in I/R injury (Chiu *et al*., 2009).

The data showed that supplying rats with dexamethasone for 3 consecutive days prior to I/R injury significantly reduced hepatic I/R injury as evidenced by reduced serum ALT, AST, hepatic MDA, MPO total nitrates/nitrites and significantly increased hepatic GSH as compared to hepatic I/R control rats. The results were in line with the prevention of PEA-induced hepatotoxicity by dexamethasone (Donald *et al*., 2003). Dexamethasone possesses pleiotropic pharmacological activities including activation of many transcription factors and anti-inflammatory stimuli, many of which could conceivably contribute to its ability to protect rat livers (Wang *et al*., 2010). The anti-inflammatory effect of dexamethasone could be attributed to interference with cytokines release. This could inhibit cells factor release and relive hepatic inflammation.

The reactive oxygen species are generated by aerobic metabolism and environmental stressors. They can chemically modify proteins and alter their biological functions and if the repair processes fail, oxidized proteins may become cytotoxic (Van der Veen *et al*., 2009). Myeloperoxidase (MPO), a heme-containing peroxidase abundantly expressed in neutrophils and monocytes while produces the powerful oxidant hypochlorous acid and is a key contributor to the oxygen-dependent microbicidal activity of phagocytes is linked to tissue damage in many diseases when it is excessive to generate MPO-derived oxidants (Hernandez *et al*., 2011). In the research, dexamethasone displayed a strong effect on MPO, demonstrating the oxidative impairment of neutrophils can be prevented by dexamethasone.

Malondialdehyde (MDA) is the principal and most studied product of polyunsaturated fatty acid peroxidation. Measurement of MDA is considered an effective marker of oxidative stress in a biological sample (Buettner, 2011). In the study, it could be showed that dexamethasone has a significant effect on MDA expression which implies dexamethasone has a strong potential to suppress oxidative stress.

The hepatoprotective effects of aspirin could be attributed to its anti-inflammatorty effects. NSAIDs modulate the risk of inflammation by inhibiting the COX enzymatic pathways necessary for synthesis of prostaglandins (Knights *et al*., 2010). This inhibition of prostaglandins, as well as decreases in epithelial proliferation and angiogenesis, coupled with increased apoptosis, results in the reduction in the inflammatory response (Jankowska *et al*., 2010). It has also been suggested that aspirin and NSAIDs, in general might play a hepatprotective role through other non-COX inhibitory pathways (Imaeda *et al*., 2009) and downregulation of proinflammatory cytokines (Leng *et al*., 2003).

Data of the present study showed that bromocriptine improved serum ALT and AST and consequently decreases hepatic I/R injury. Markedly reduced the oxidative stress biomarker MDA in serum and markedly increased hepatic GSH content as compared to control I/R injury. The inflammatory mediators MPO and total nitrate/nitrite in liver were also significantly reduced as compared to hepatic I/R control injury. A marked improvement of histopathological findings was observed. The ability of bromocriptine to ameliorate hepatic injury could be attributed to its observed effects on attenuating oxidative stress markers. In the same context, Li *et al*. (2011) reported that bromocriptine significantly decreased LDH and MDA levels, increased SOD activity, reduced morphological injury of cardiomyocytes, increased the cell viability and decreased apoptosis.

Another possible explanation for the hepatoprotective effects of bromocriptine could be attributed to the activation of dopamine D2 receptor which significantly inhibits apoptosis induced by ischemia/reperfusion injury, possibly through suppression of the activation of adenylate cyclase, down-regulation of cyclic AMP (cAMP) levels, then inhibition of the activation of Protein Kinase A (PKA), inhibition of L-type voltage-gated channels and finally decrease (Ca^{2+}) (Gingrich and Caron, 1993).

CONCLUSION

The present data supports the beneficial effects of fish oil, allopurinol and verapamil in management of Ischemia/Reperfusion (I/R) as a liver injury model. The clinical significance of these results must be elucidated in further studies.

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