The Lung Endothelin System: a Potent Therapeutic Target with Bosentan for the Amelioration of Lung Alterations in a Rat Model of Diabetes Mellitus

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Background:

Endothelial dysfunction underlies lung and other organ complications developing in associated with diabetes. The endothelium is a dynamic organ that releases several substances. Studies have shown that the endothelin plays significant roles in the development of diabetic complications. Endothelin 1 (ET-1), released by the endothelial cells, is the most powerful known vasoconstrictor agent and exhibits vasoconstrictor and proliferation-stimulating effects on the smooth muscle cells of the pulmonary arteries. There is no study about the role and importance of endothelin receptors in diabetes-related pulmonary injury.

Objective:

The aim of this study was to show the effect of a new mechanism on endothelin receptors in the physiopathology of diabetes-related pulmonary injury, and to reveal the effect of the endothelin receptor antagonist bosentan on improvement of this physiopathology via molecular, biochemical, and histopathological terms analyses.

Method:

The rats were separated into four groups. There were 6 rats in each group. Group 1 (SHAM): control group; Group 2 (DM): streptozotocin 60 mg/kg (i.p.); Group 3 (DM+BOS-1): streptozotocin 60 mg/kg (i.p.)+bosentan 50 mg/kg peros; Group 4 (DM+BOS-2): streptozotocin 60 mg/kg (i.p.)+bosentan 100 mg/kg peros. The bosentan treatment was initiated immediately after occurred STZ induced diabetes and continued for 6 weeks. The nondiabetic healthy group and diabetic control group were exposed to only 0.9% saline for 30 days (2 ml/day).

Superoxide dismutase activity (SOD), glutathione levels (GSH), and malondialdehyde levels (MDA) from each sample supernatant and standard were measured in the grinded lung tissue. Relative ET-1, ET-A receptor, ET-B receptor, tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β) expression analysis were performed. Also, lung tissue samples were obtained by histopathological examinationation.

Results:

SOD activity was observed to statistically decrease in the diabetic groups when compared to the healthy group, as shown in Table. SOD activity was seen to significantly improve in the groups treated with bosentan. When administered bosentan 50 mg/kg in treatment group of our study it was not observed significantly difference with GSH levels of diabetic groups, while using 100 mg/kg doses of bosentan significantly increases the level of GSH and especially it was found that this value is very close with the healthy group. It was observed that MDA levels in lung tissue of diabetic rats increased dramatically compared to MDA levels of the healthy group. ET-1 gene expression increased in the STZ-induced DM groups compared to the control groups. Compared to the control groups, ET-A and ET-B receptor gene expression increased in the STZ-induced DM groups (Fig.1). Compared to the control group, TNF-α mRNA level was significantly higher in the DM group. TGF-β gene expression increased 2.20-fold in the DM groups compared to the control groups (Fig.2).

Table: Effects of Bosentan treatments on changes levels of GSH, MDA and activities SOD in lung of rats

	SOD (U/mg protein)	GSH (nmol/mg protein)	MDA (nmol /mg protein)
HealthyGroup	13,19 ± 4,42**c**	2,84 ± 1,02**c**	1,10 ± 0,51**a**
Diabet Control	6,80 ± 1,40 **a**	1,38 ± 0,67**a**	3,17 ± 0,76**c**
Diabet + BOS 50 mg/kg	10,05 ± 2,17**b**	1,68 ± 0,81**a,b**	1,87 ± 0,47**b**
Diabet + BOS 100 mg/kg	10,08 ± 1,73**b**	2,36 ± 0,70**b,c**	1,49 ± 0,43 **a,b**

Interalveolar edema, thickness in interalveolar septum, hemorrhage, intraparenchymal vascular congestion, interstitial inflammation, and emphysematous changes were severe in nontreated diabetic rats (Fig.3). Interalveolar edema, thickness in interalveolar septum, hemorrhage, interstitial inflammation, and emphysematous changes in the BOS-1-treated group were less severe than in nontreateddiabetic rats. In the BOS-2-treated group, only thickness in interalveolar septum and slight interstitial inflammation were evident (Fig.3).

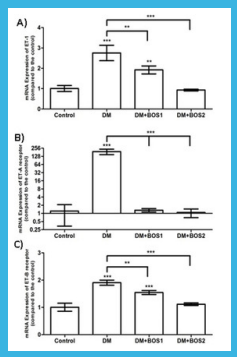

Figure 1

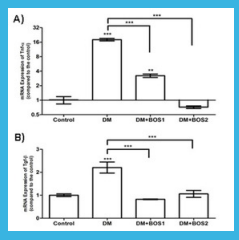

Figure 2

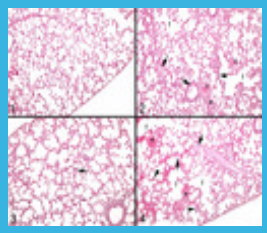

Figure 3

Conclusion:

Following bosentan therapy, improvement in endothelial dysfunction, histopathological marked, and a decrease in cytokine levels were recorded, and the antioxidant balance progressed. With its multiple effects, bosentan therapy may be an effective option against lung complications that may develop in association with diabetes