Oxidative DNA damage and antioxidant status in the kidney of diabetic rats: protective effect of losartan

[1]E. Bigagli, [2]F. Tarantini, [2]C. Di Serio, [1]L.Raimondi,[1]M. Lodovici

[1]Dept. of Neurofarba: Section of Pharmacology and Toxicology, University of Florence, Italy
[2]Dept. of Experimental and Clinical Medicine, University of Florence, Italy.

Type 2 diabetes has been associated with increased risk of several cancers such as breast, kidney and gastrointestinal. The underlying mechanisms have been debated and remain unclear. Hyperglycemia and possibly hyperinsulinemia, are supposed to be risk factors for cancer in diabetes. Hyperglycemia is a well-known stimulator of ROS production, which in turn triggers several detrimental processes, including inflammation, altered activity of protein kinase C isoforms, and advanced glycation end-product formation. The mutagenic properties of oxidatively damaged DNA and increased oxidative stress might be considered among the reasons for increased risk of cancer in diabetes. We previously reported an increase in lipid and protein oxidation damage in the diabetic kidney which was reduced by losartan treatment, an AT1 antagonist. In this new study we investigated whether streptozotocin (STZ)-induced diabetes induces nuclear DNA oxidative damage in the kidney and the effect of losartan on hyperglycemia-induced DNA oxidation. We also measured plasma levels of Adiponectin (Adp), a hormone secreted by adipose tissue that acts as negative regulator of diabetes and seems to inhibit cancer development in normoglycemic and diabetic rats. Two weeks after STZ injection, oxidative DNA damage, measured as 8-OHdGuo levels, was significantly greater (about six folds) in diabetic than in normoglycemic rats. The 8-OHdGuo levels were significantly reduced in the kidney of diabetic rats treated with 20 mg/kg/day of losartan for 3 weeks in comparison to not treated ones, without modifying plasma glycemia. The antioxidant capacity, measured as FRAP values, were significantly lower in diabetic rats than in normoglycemic group. Losartan treatment prevented diabetes-induced FRAP reduction. Hyperglycemic rats had plasma Adp levels significantly ($P<0.001$) lower than those measured in normoglycemic group. An inverse correlation was found between circulating Adp levels and oxidative DNA damage in renal tissue from both normoglycemic and diabetic rats. ($r= 0.84$, $n= 12$, $p<0.001$; $r=0.71$, $n=21$, $p< 0.001$ respectively). In conclusion, our data indicate that diabetes results in the disruption of the fine balance between oxidant and antioxidants status leading to an increased nuclear oxidative DNA damage, a risk factor for carcinogenesis.