Involvement of iron overload in hypertensive nephropathy: effects of the iron chelator deferoxamine

P. Gelosa[1], A. Pignieri[1], E. Gianazza[1], S. Criniti[1], U. Guerrini[1], M.D. Cappellini[2], E. Tremoli[1,3], L. Sironi[1,3]

[1]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano
[2]Dipartimento di Medicina Interna, Medicina Interna 1A, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan
[3]Centro Cardiologico Monzino IRCCS, Milan, Italia

Background and aim: Iron is the most abundant metal in mammalian cells, and plays a pivotal role in many metabolic processes. Dysregulated iron homeostasis is involved in the etiology of a number of pathological processes including renal diseases. ***Methods and Results*** Longitudinal magnetic resonance imaging scans of salt-loaded spontaneously hypertensive stroke-prone rats (SHRSP), an animal model that spontaneously develops hypertensive nephropathy, showed a decrease in renal and hepatic T2* signal intensity (SI) - a sign of iron accumulation - of respectively 42.3±2.5% ($p<0.01$) and 60.4±15.1% ($p<0.01$) in comparison with SHRSP fed a standard diet. This was accompanied by the development of renal inflammation and oxidative stress (as evaluated by immunohistochemical and proteomic analyses), mitochondrial dysfunction, massive proteinuria and sustained intravascular hemolysis with the subsequent depletion of plasma haptoglobin, which was responsible for the renal uptake of hemoglobin and iron accumulation. In order to investigate the role of iron in these pathological processes, we subcutaneously treated the salt-loaded rats with the iron chelator deferoxamine (200 mg/kg/day). The pharmacological treatment prevented iron tissue accumulation, as indicated by the increase in renal and hepatic T2* SI of respectively 120.0±10.1% ($p<0.01$) and 73.9±4.4% ($p<0.01$) in comparison with salt-loaded rats treated with vehicle alone. Deferoxamine also preserved renal morphology and function, decreased the renal infiltration of ED-1-positive macrophages/monocytes, and the expression of MCP-1 and TGF-beta mRNA, reduced the level of reactive oxygen species, and improved the activity of mitochondrial cytochrome c oxidase.
Conclusion These data suggest an involvement of iron dysmetabolism in the development of hypertensive nephropathy and indicate new directions for the pharmacological prevention/treatment of hypertensive renal diseases.