EFFECT OF A RECOMBINANT MANGANESE SUPEROXIDE DISMUTASE ON PREVENTION OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

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INTRODUCTION

Contrast media-induced nephropathy (CIN) is an acute deterioration of renal function following administration of contrast media (CM), due to combined hypoxic and toxic renal parenchymal injury, mediated, to large extent, by an increased production of reactive oxygen species (ROS) within the kidney(1). The different isoforms of superoxide dismutase (SOD) have recently attracted researchers' attention for a possible protective role in CIN. We have recently isolated a novel isoform of a recombinant Manganese Superoxide Dismutase (rMnSOD), derived from a human established liposarcoma cell line (LSA), which shares the same ability of physiological SODs in transforming free radicals into hydrogen peroxide(2), but shows peculiar structural and functional properties. The rMnSOD, in fact, is linked to an uncleaved terminal peptide sequence (leading peptide) which, at difference with commercial SODs, allows the molecule to enter inside the cells after its administration(3). rMnSOD has been shown to be very effective in scavenging both intra- and extracellular O_2^-, hence improving pathological conditions associated with increased oxidative stress(4). Additionally, rMnSOD shows an excellent organ bioavalaibility and, therefore, seems well suited for correcting also renal oxidative stress.

AIM OF STUDY

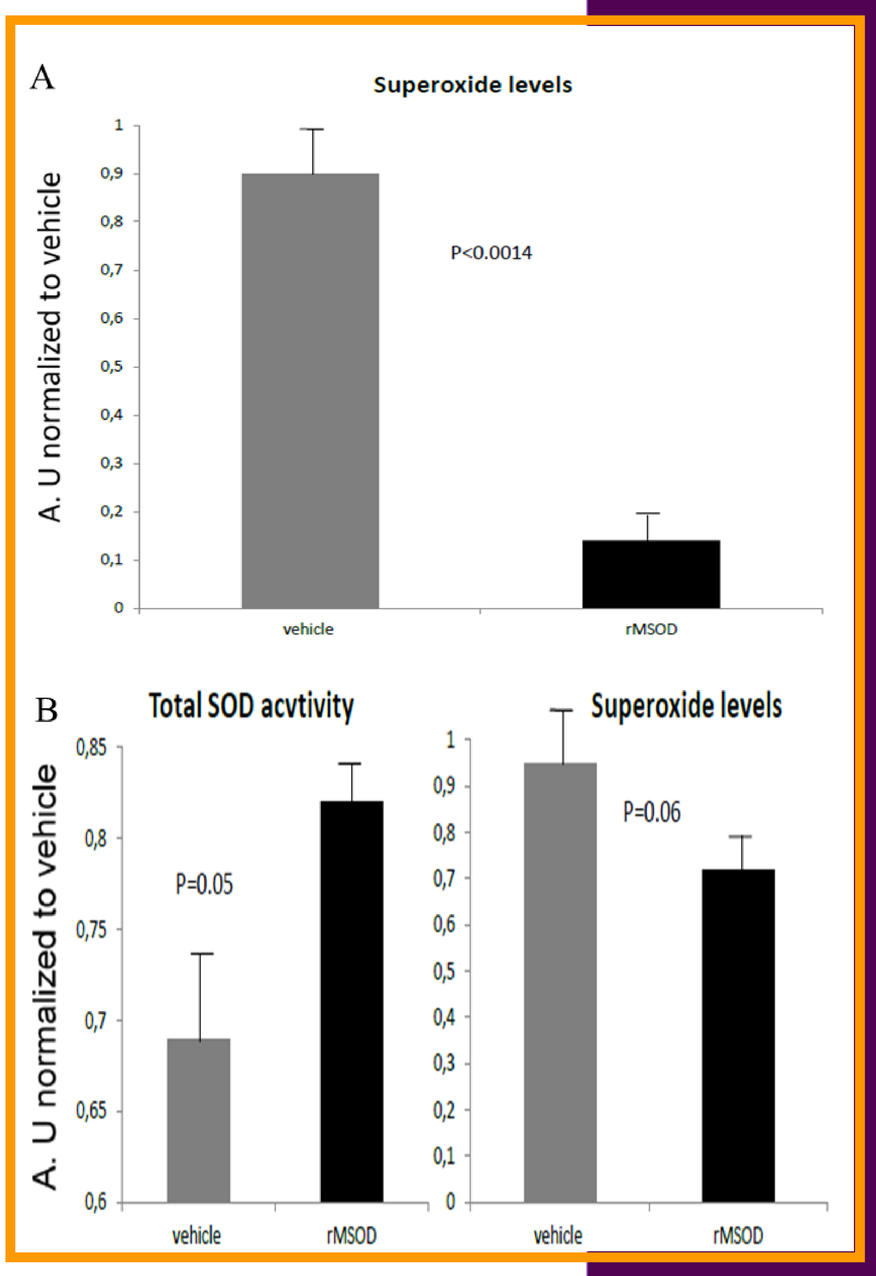
Aim of this study was to evaluate whether rMnSOD could provide an effective protection against CIN.

METHODS

We studied the effects rMnSOD on oxidative damage in a rat model of CIN: 27 uninephrectomized rats were randomly assigned to 3 experimental Groups: Group HCM (n=9), rats treated with CM; Group SOD (n=10), rats treated with CM and rMnSOD; Group CON (n=9), control rats treated with the vehicle of CM. We evaluated and compared glomerular filtration rate (GFR), rMnSOD presence and activity in the kidney, ROS production and renal histology in the rats of the 3 groups.

RESULTS

In comparison to rats pre-treated with vehicle, the rats of SOD group showed significantly reduced intrarenal O2- levels (-84%; p<0.0001, A) and a significant increase in SOD activity in kidneys (+16%; p=0.05, B). ROS production in rats of Group HCM was almost doubled compared to rat of Group CON (12030 ± 300 vs 5286 ± 500 IF/gr of tissue/µg of proteins; p<0.01, C). Conversely, in rats of Group SOD ROS production overlapped those of Group CON (4579 ± 230 vs 5286 ± 500 IF/gr of tissue/µg of proteins, C). Glomerular filtration rate (GFR) averaged 0.92 ± 0.2 ml/min/100 g b.w. in control rats and was significantly depressed by 70% in rats of Group HCM (0.27 ± 0.1 ml/min/100 g b.w.; p<0.001 *vs* Group CON). Pre-treatment with rMnSOD determined a consistent preservation of renal function after the toxic insult, with GFR values significantly higher than those of Group HCM (0.66 ± 0.1 ml/min/100 g b.w., p < 0.05 vs HCM, but NS vs CON, C). All rats in group CM developed tubular necrosis, proteinaceous casts, and medullary congestion. Pre-treatmentwith rMnSOD attenuated the development of all these lesions, although significant protective effectswere observed only in tubular necrosis (P = 0.001) and proteinaceous cast (P < 0.001).



C

	BW g	KW g	BP mmHg	Ht %	GFR ml/min/100g bw	FF %	RPF ml/min/100g	RBF ml/min/100g	RVR mmHg/ml/min	ROS IF/gr of tissue µg of proteins /
CON (*n* = 9)	319.7±42.3	1.541±0.1	110±9	43.0±2.0	0.92±0.2	27.5±3.4	3.4±1.5	6.14±2.2	18.1±8.6	5286±500
HCM (*n* =8)	289.7±32.3	1.641±0.1	106±9	42.6±2.4	0.27*±0.1	NA	NA	NA	NA	12030±300#
SOD (*n* =10)	310.1±32.3	1.741±0.1	112±11	43.0±2.0	0.66†±0.1	22.8*±2.2	2.76§±1.1	4.41§±1.9	26.1±9.6	4579 ± 230

Renal hemodynamics and ROS quantification in the different groups under study

CONCLUSIONS

Our data indicate that rMnSOD is able to greatly reduce renal oxidative stress, and its associated reduction of GFR following CM administration. In addition, contrast-induced proteinuria, proteinaceous cast and tubular necrosis are restored by rMnSOD.These preliminary data suggest that the use of rMnSOD may open new perspectives in the treatment of CIN, as well as in many pathological conditions associated with increased oxidative stress.

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