Reduced NO production rapidly aggravates renal function through the NF-κB/ET-1/ETA receptor pathway in DOCA-salt-induced hypertensive rats

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It has been reported that endothelin-1 (ET-1) overproduction and reduced nitric oxide (NO) production are closely related to the progression of renal diseases. In the present study, we examined the interrelation between ET-1 and NO system using rats treated with the combination of deoxycorticosterone acetate (DOCA)-salt and a non selective NO synthase inhibitor N□-nitro-L-arginine (NOARG). Male Sprague Dawley rats (6 weeks old) were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and the right kidney was removed via a right flank incision. After a 1-week postsurgical recovery period, rats were separated into a sham-operated group (n=9) and a DOCA-salt group. Two weeks after DOCA-salt (15 mg/kg, s.c. plus drinking water containing 1% NaCl) treatment, the administration of NOARG (0.6 mg/ml in the drinking water, n=8) for 3 days drastically developed the severe renal dysfunction and tissue injury. In these rats, ET-1 mRNA expression was additionally enhanced in the kidney compared to the rats treated with DOCA-salt alone (n=9), and a selective ET_A receptor antagonist ABT-627 (10 mg/kg/day, p.o., n=9) completely prevented renal damage. Thus, these findings indicate that endogenous NO functions as a protective factor against the development of renal disorders in DOCA-salt rats at 2 weeks. On the other hand, as our previous studies have shown that NO modulates the ET-1 production via the regulation of nuclear factor (NF)-□B activation in vitro, we next determined if NF-κB pathway contributes to the renal dysfunction observed in above rats. Two weeks after DOCA-salt treatment, the administration of NOARG for 3 days increased NF-□B DNA binding activity in the kidney. Additionally, a NF-□B inhibitor pyrrolidine-dithiocarbamate (100 mg/kg/day, i.p., n=6) completely improved renal dysfunction and tissue injury and suppressed renal ET-1 production. Taken together with our findings, it is most likely that NF-□B/ET-1/ET_A receptor-mediated actions are responsible for the increased susceptibility to DOCA-salt induced renal injuries in the case of reduced NO production.