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VASCULAR HEME OXYGENASE-1 AMELIORATES
ALDOSTERONE-ELICITED ARTERIAL INJURY IN MICE

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Heme oxygenase is a microsomal enzyme that catalyzes the degradation of heme into biliverdin, which is subsequently reduced to bilirubin, free iron and carbon monoxide (CO). Induction of heme oxygenase-1 (HO-1) has been potentially associated with cellular protection, especially against oxidative insults. Using smooth muscle cell-directed HO-1 over-expression mice (HO-1 Tg mice), we investigated the organ-protective effect of HO-1 against aldosterone (ALD), which has been shown to play a critical role in the cardiovascular injury. With the administration of ALD on a high-salt diet for 14 days, blood pressure levels measured by tail-cuff method between wild type (WT) and HO-1 Tg mice increased almost identically. In WT mice, ALD/salt loading stimulated both urinary excretion of 8-hydroxydeoxyguanosine and isoprostane, makers of oxidative stress which were coincided with the increased immunostaining 3-nitrotyrosine, the metabolites of reactive oxygen species, in the coronary artery of ALD/salt-treated mouse, as compared with those of HO-1 Tg mice. Inflammatory changes, including MCP-1 and COX-2 expression and infiltration of leukocytes determined by immunostaining and neointimal hyperplasia with perivascular fibrosis were markedly suppressed in HO-1 Tg mice, as compared with those of WT mice. We conclude that vascular HO-1 counteracts ALD-elicited arterial injury through the inhibition of oxidative stress production and inflammatory reactions.

Key Words: Heme Oxygenase, Oxidative Stress, Inflammation

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HYPOKALEMIA IN THE ABSENCE OF ELEVATED
ALDOSTERONE AMELIORATES RENAL DAMAGE IN
STROKE PRONE SPONTANEOUSLY HYPERTENSIVE
RATS (SHRSP)

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We have previously shown that aldosterone (ALDO), not Ang II, can reverse the vascular protective effects of adrenocortical in SHRSP. However, aldosterone infusion can result in hypokalemia, which may mediate or contribute to renal injury. In the present study we examined whether hypokalemia, per se, in the setting of severe hypertension would promote renal injury. Male SHRSP were maintained on a normal (1.1% K\textsubscript{2}H\textsubscript{2}O\textsubscript{3}) diet. All groups showed mild proteinuria, indicative of renal damage, on day 0 (Table). Elevated urinary protein excretion was unaffected by 1.1% K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} or 0.37% K\textsubscript{2}H\textsubscript{2}O\textsubscript{3}, but was significantly reduced by 0.01% K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} on day 14 (22.55 mg/day, p<0.001) and on day 28 (31.5 mg/day, p<0.001). Systolic blood pressure did not differ among the groups on day 14 but was significantly reduced in the 0.01% K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} group on day 28 (Table). At that time, serum K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} levels were significantly reduced and urinary K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} excretion was negligible in the low K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} group (Table). Serum Na\textsubscript{2} did not differ among the groups and none of these animals showed stroke signs as a consequence of these dietary K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} manipulations. 0.01% K\textsubscript{2}H\textsubscript{2}O\textsubscript{3}, but not 0.37% dietary K\textsubscript{2}H\textsubscript{2}O\textsubscript{3}, was associated with highly significant increases in plasma renin activity and reductions in plasma ALDO. Thus, despite marked hypokalemia, increased plasma renin activity and elevated blood pressure, low dietary K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} diminished urinary protein excretion. The data indicate that hypokalemia, per se, does not provokes renal injury in SHRSP. Rather, hypokalemia-induced reductions in ALDO levels may be responsible for the ameliorative effects of low dietary K\textsubscript{2}H\textsubscript{2}O\textsubscript{3} on urinary protein excretion and blood pressure in these animals.

Key Words: Hypokalemia, Renal Damage, Aldosterone

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ACTIVATION OF THE INTRARENAL RENIN-
ANGIOTENSIN SYSTEM IN DIABETIC WOMEN
INGESTING THE ORAL CONTRACEPTIVE

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Diabetes mellitus (DM) is the leading cause of end-stage renal disease (ESRD) in the U.S. Intra renal renin angiotensin system (RAS) activation is believed to be a risk factor for diabetic nephropathy. We have previously reported reduced renal blood flow in healthy women using first-generation estrogen- and progestin-containing oral contraceptives (OCs), reflecting renal vasoconstriction due to activation of the RAS. In this study, activation of the RAS was investigated in 39 diabetic and 51 healthy women, some of whom were taking newer generations of the OC containing smaller amounts of estrogen (20-35 μg), by measuring renal plasma flow (RPF) as para-aminophippurate (PAH) clearance while subjects were in balance on a high-salt diet. We compared baseline RPF and its response to 25 mg captopril PO in 28 diabetic OC users and 11 diabetic OC users, and 41 healthy OC nonusers and 10 healthy OC users. Diabetic OC users had a significantly larger vasodilator response to captopril than did diabetic OC nonusers (84 ± 12.7 vs. 49 ± 9.1 mL/min/1.73m\textsuperscript{2}, p<0.01), as did healthy OC users compared to healthy OC nonusers (69 ± 33.1 vs. 9 ± 10.3 mL/min/1.73m\textsuperscript{2}, p=0.004) (Figure 1). Diabetic OC nonusers demonstrated the anticipated larger RPF response to ACE-inhibition in comparison to their healthy counterparts (p=0.002).

Twenty-four hour urinary protein excretion tended to be greater in the diabetic OC user group (94±43.9 mg/24h) than in the diabetic OC nonuser group (75±40.9 mg/24h), but the difference did not achieve statistical significance (p=0.3). Given the association between an activated intrarenal RAS and diabetic nephropathy, OC use in the setting of DM warrants further study. Caution and surveillance should be applied with chronic administration of the OC in the DM population.

Fig 1. Renal plasma flow response to captopril.

Key Words: Diabetes Mellitus, Oral Contraceptive, Angiotensin II