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Midkine regulates blood pressure through cytochrome P450-derived eicosanoids

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Background: Endothelial dysfunction leads to hypertension (HTN), cardiovascular and kidney diseases, and is accompanied by deregulated production of endothelial factors. Similarly to nitric oxide(NO), endothelium-derived hyperpolarizing factor (EDHF) acts as an important vasodilator. Although it has been reported that the cytochrome P450-derived epoxyeicosatrienoic acids (EETs) can function as EDHFs, its biological/clinical significance remains largely unexplored. The growth factor midkine (MK) has been implicated in various biological and pathological events, and involved in cardiac and renal injury. We recently reported that MK enhances HTN in the renal ablation model by upregulation of pulmonary angiotensin converting enzyme (ACE). Since MK is expressed by endothelial cells, we hypothesized that MK might play a fundamental role in blood pressure (BP) to regulate endothelial factors aside from its role via the renin-angiotensin system (RAS).

Methods: Wild-type mice (WT) and MK-deficient mice (MK-KO) were treated with the NO synthase inhibitor L-NAME and unilateral nephrectomy (L+UNx). They were measured BP and sacrificed on 4 months. The HTN of WT mice with L+UNx was treated by MK antibody (MK-Ab). To clarify the EETs' involvement, WT and MK-KO mice were administered charybdotoxin, K_{Ca} channel blocker, and 14, 15-EEZE, 14,15-EET competitive analogue, respectively and recorded BP using radio-telemetry systems. Primary renal endothelial cells were isolated from WT and MK-KO, and evaluated EETs.

Results: In the L+UNx group, BP of WT mice developed marked HTN, while MK-KO mice exhibited normotension. Systemic administration of MK-Ab significantly suppressed the BP elevation induced by L+UNx. Proteinuria and glomerular sclerosis were also attenuated in MK-KO. Urine nitrate/nitrite was decreased to the same extent in both WT and MK-KO with L+UNx. There were no genotypic differences in eNOS and cGMP. Taken together, although MK was required for the development of HTN in a model of NO deficiency, the NO axis itself did not mediate hypertensinogenic action of MK. We investigated some vascular tone controlling factors. The RAS, endothelin, and PGI_2 were similar in WT and MK-KO. Finally, we found that MK suppressed the generation of EETs. 14,15-DHET, 14,15-EET metabolites, were increased in urine and medium of primary endothelial cells of MK-KO compared to WT. The EETs pathway blockage by charybdotoxin or 14, 15-EEZE elevated BP higher in MK-KO than in WT. EETs dominantly regulated BP in MK-KO, which could be reproduced by MK Ab administration to WT. MK administration to MK-KO recapitulated the BP control observed in WT.

Conclusion: The MK/EETs pathway is physiologically engaged in the BP control. This pathway could be a target for the treatment of HTN complicated by endothelial dysfunction.

Figures:

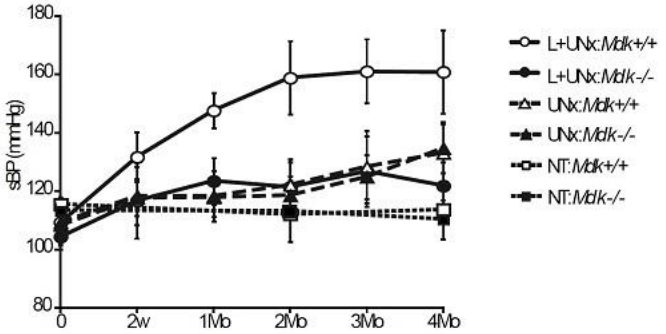

Figure Hypertension induced by a NOS inhibitor was attenuated in *Mdk-/-* mice. (**A**) Systolic blood pressure (sBP) was measured by the tail-cuff method in conscious mice at 0 and 2 weeks, and at 1, 2, 3, and 4 months after uni-nephrectomy with L-NAME administration (L+UNx), uni-nephrectomy alone (UNx), or no treatment (NT). Data are presented as the mean ± SEM (L+UNx: *Mdk*+/+, n=7; L+UNx: *Mdk-/-*, n=8; UNx: *Mdk*+/+, n=10; UNx: *Mdk-/-*, n=10; NT: *Mdk*+/+, n=8; NT: *Mdk-/-*, n=6). p=0.002 (L+UNx: *Mdk*+/+ vs. L+UNx:*Mdk-/-*).

Keywords: endothelial dysfunction, hypertension