KSN 2020
FULLY VIRTUAL MEETING

Abstract Submission No. : IL-9049

Lipid induced kidney injury: a role of renal renin angiotensin system

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Lipotoxicity plays an important role in the pathogenesis of kidney injury. Accumulation of saturated free fatty acids in tubular cells produces significant cellular dysfunction and injury. We have recently demonstrated that blockade of renin-angiotensin system (RAS) with direct renin inhibitor aliskiren, angiotensin II type 1 receptor blocker valsartan, or chymase inhibitor chymostatin effectively attenuated tubular epithelial cell injuries induced by saturated fatty acid palmitic acid (PA) or high-fat diet (HFD) in mice. As an alternative pathway of the RAS, the role of angiotensin 1-7 (Ang (1-7)) and its G-protein coupled receptor Mas has also been examined. In mice fed with HFD, the protein abundance of markers of autophagy, endoplasmic reticulum stress (ER stress) and apoptosis was dramatically increased in the kidney cortex, which was markedly prevented by Mas deletion or Mas receptor antagonist A779. In human proximal tubular HK2 cells, PA-induced autophagy and ER stress was aggravated by Mas agonists Ang (1-7) or AVE0991, but attenuated by A779 or Mas knockdown. Stimulation of Mas resulted in elevated intracellular calcium levels [Ca2+]i in HK2 cells treated with PA, whereas inhibition or knockdown of Mas decreased [Ca2+]i. Mitochondrial outer membrane located voltage-dependent anion channel (VDAC1) was markedly upregulated in HK2 cells treated with PA, which was associated with impaired mitochondrial morphology and depolarization. These were enhanced by AVE0991 and suppressed by A779 or Mas knockdown. Mas knockdown in HK2 cells prevented impaired interactions among VDAC1, autophagy adaptor P62, and ubiquitin, induced by PA, leading to a potential ubiquitination of VDAC1. In conclusion, Mas receptor mediated lipid-induced impaired autophagy and ER stress in the kidney, likely contributing to tubular injuries in obesity-related kidney diseases.