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The comparative effect of APX-115, a First in Class pan-Nox inhibitor and angiotensin receptor blockade on diabetic nephropathy in type 2 diabetic mice

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Background: Since all components of Nox isoforms are expressed in various parts of the kidney, targeting all Nox components may be a promising therapeutic strategy to ameliorate renal damage from ROS in diabetic nephropathy. Recent studies have suggested the importance of renal Nox in the progression of diabetic nephropathy. Therefore, we investigated the comparative effect of a First in Class pan-Nox inhibitor APX115 and L158809 (ARB) and their combination on diabetic nephropathy in type 2 diabetic mice.
Methods: 8 to 10 week old db/m and db/db mice were treated with APX-115 for 12weeks. APX-115 was administered by oral gavage at a dose of 60mg/kg/day. To compare the effects of APX-115 with ARB, other group was treated with LC158809 (1.5mg/kg/d) or treated with both APX-115 and LC158809 for 12 weeks.
Results: As expected, diabetic mice showed significantly higher levels of body weight, fasting glucose levels, HbA1c, food and water intake compared with non diabetic db/m mice. Interestingly, both APX-115 group and ARB group showed significantly improved insulin resistance determined by plasma insulin and HOMA-IR and lipid abnormality. In addition, both APX-115 group and ARB group showed similar improvement in oxidative stress (serum and urine 8-isoprostane level). Most importantly, both APX-115 group and ARB group showed a significant decrease in urinary albumin excretion with a similar potency, associated with decreased urinary loss of nephrin. In renal tissues, renal Nox 1, 2 and 4 protein expression was decreased in APX-115 group, but not in ARB group. Although there were no additive beneficial effects in insulin resistance, oxidative stress and lipid abnormality, combined treatment with APX-115 and ARB showed additive renoprotective effects such as urinary albumin excretion, creatinine clearance and structural changes such as mesangial expansion.
Conclusion: Our results provide evidence that pan-Nox inhibition by APX-115 may have similar renoprotective potential with ARB, and combination therapy with APX-115 and ARB may have better renoprotective potential in diabetic nephropathy. These findings suggest that an agent that simultaneously inhibits various Noxs therefore holds a considerable promise as a new antidiabetic drug.

Keywords: angiotensin II receptor blockade, diabetic nephropathy , pan-Nox inhibitor