Establishment of high HPRT activity *Urat1-Uox* double knockout mouse and the effects of xanthine oxidoreductase inhibitor

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It is known that there are species differences in the purine metabolic system between humans and rodents (e.g. urate oxidase (Uox), and hypoxanthine phosphoribosyltransferase (HPRT), etc.). URAT1 (SLC22A12) is renal urate (UA) reabsorption transporter and the target for UA-lowering therapies. In humans, URAT1 deficiency has a significant UA-lowering effect (ULE), but not in *Urat1*-knokout (KO) mice. The aim of this study is the establishment and urate kinetic profiling of high HPRT activity *Urat1-Uox* double knockout (DKO) mice and the investigation of the effect of xanthine oxidoreductase inhibitor (XOI), topiroxostat in this model mice. Topiroxostat 1 mg/kg (Top) was administered to DKO mice for 7 days by feeding diet. Oxypurines (UA, hypoxanthine and xanthine) and creatinine in plasma and urine were measured by HPLC. DKO mice showed a significant decrease in plasma UA levels, increased fractional excretion of UA (FE_{UA}), and enhanced Top-induced ULEs, compared with *Uox*-KO only. Thus, high HPRT activity seems to be important for producing ULE by URAT1 inhibition. The combination therapy of URAT1 inhibition and XOI showed an effective ULEs, suggesting that it is useful for the treatment of hyperuricemia.