Metformin Reduces the Intestinal Absorption of Vitamin B1 (Thiamine) via Organic Cation Transporter 1, OCT1 (SLC22A1)
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Purpose
Lactic acidosis is a rare adverse effect of metformin, the most widely prescribed anti-diabetic drug. Chronic treatment with metformin and its analog, phenformin, has been reported to reduce the systemic plasma levels of several members of the vitamin B family, notably, vitamin B1 (thiamine) and B12 (cobalamin). Thiamine plays a critical role in glucose metabolism, and thiamine deficiency has been reported to lead to lactic acidosis. Our laboratory recently identified thiamine as a major endogenous substrate for OCT1, which is the major hepatic transporter of metformin and may also contribute to its intestinal disposition. We hypothesized that metformin and phenformin inhibit thiamine uptake via OCT1 through a competitive mechanism, which may contribute to its adverse effect in producing lactic acidosis.

Methods
Thiamine uptake and metformin-thiamine interaction studies were performed using [3H]-thiamine in OCT1 overexpressing HEK cells. In vivo studies of the acute effect of metformin on thiamine disposition were performed in male wildtype and Oct1 knockout mice through intravenous dosing of [3H]-thiamine and metformin. Chronic effect of metformin on thiamine disposition was studied in wildtype mice after 7 days of intraperitoneal doses (100mg/kg). Thiamine and its metabolites in plasma were analyzed by LC-MS/MS.

Results
Metformin and phenformin significantly reduced thiamine uptake in OCT1 expressing cells (IC50: Metformin=1.4mM; phenformin=0.07mM). The levels of total thiamine products in the intestine of Oct1 knockout mice were reduced in comparison to wildtype mice after intravenous dosing of [3H]-thiamine (reduction: duodenum: 90%; jejunum: 87%; ileum: 80%). Co-dosing metformin with thiamine intravenously resulted in significant lower total thiamine products in the intestine (reduction: duodenum: 42%; jejunum: 40%; ileum: 35%) than in mice dosed with thiamine alone. Chronic treatment of metformin was associated with reductions in systemic plasma levels of thiamine (saline group: 402±42ng/ml; metformin group: 187±53ng/ml; p<0.01) and its active metabolite, TPP (saline group: 8.2±2ng/ml; metformin group: 4.8±0.8ng/ml; p<0.05).

Conclusion
Metformin reduces thiamine uptake via OCT1 in vitro and in mice. Reduced thiamine levels may contribute to the development of lactic acidosis.