URAT1-selective inhibition ameliorates insulin resistance by attenuating diet-induced hepatic steatosis and BAT whitening in mice

Y. Tanaka, T. Nagoshi, A. Yoshii, Y. Oi, H. Takahashi, H. Kimura, Y. Kashiwagi, T.D. Tanaka, M. Yoshimura

Jikei University School of Medicine (Tokyo), Tokyo, Japan
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Background: Accumulating evidence suggests that high uric acid is strongly associated with obesity and metabolic syndrome and drives the development of non-alcoholic fatty liver disease (NAFLD) and insulin resistance. Although urate transporter-1 (URAT1), which is primarily expressed in the kidney, plays a critical role in the development of hyperuricemia, its pathophysiological implication in NAFLD and insulin resistance remains unclear.

Objectives: We hypothesizes that URAT1 plays an important role in obesity-induced metabolic disorders, and URAT1-selective inhibitor treatment ameliorates systemic insulin resistance, NAFLD and adipose tissue dysfunction using diet-induced obese mice.

Methods: Mice fed a high-fat diet (HFD) for 16 to 18 weeks or a normal-fat diet (NFD) were treated with or without a novel oral URAT1-selective inhibitor (dotinurad [50 mg/kg/day]) for another 4 weeks.

Results: Dotinurad administration significantly ameliorated HFD-induced obesity and insulin resistance. We found that URAT1 was also expressed in the liver and brown adipose tissue (BAT) other than kidney. HFD markedly induced NAFLD, which was characterized by severe hepatic steatosis, as well as the elevation of serum ALT activity and tissue inflammatory cytokine genes (Ccl2 and TNFα), all of which were attenuated by dotinurad. Likewise, HFD significantly increased URAT1 expression in BAT, resulting in the lipid accumulation (whitening of BAT) and increased production of tissue reactive oxygen species, which were reduced by dotinurad via UCP1 activation.

Conclusions: A novel URAT1-selective inhibitor, dotinurad, ameliorates insulin resistance by attenuating hepatic steatosis and promoting rebrowning of lipid-rich BAT in HFD-induced obese mice. URAT1 serves as a key regulator of the pathophysiology of metabolic syndrome, and may be a new therapeutic target for insulin-resistant individuals, particularly those with concomitant NAFLD.