Antibiotic-induced depletion of gut microbiota increases systemic exposure of clopidogrel active metabolite in type 2 diabetic rats

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Abstract

Background and Purpose: The current study investigated whether the manipulation of gut microbiome through treatment with an antibiotic cocktail can alter the bioavailability of clopidogrel active metabolite (Clop-AM) in T2DM rats. Experimental Approach: Control and T2DM rats were orally administered with either vehicle or an antibiotic cocktail containing ampicillin, neomycin, metronidazole, and vancomycin for 5 consecutive days. The levels of clopidogrel (Clop) and its metabolites were measured by LC-MS/MS. Biochemical parameters, liver microsome metabolism, mRNA, protein or activity of Clop- metabolizing enzymes and transporter, and 16S rRNA sequence of fecal samples were analyzed to explain any altered pharmacokinetic profile of Clop-AM. Key Results: Antibiotic administration markedly alleviated T2DM rats' phenotypes including hyperglycemia, hyperlipidemia, insulin resistance, liver dysfunction and inflammation. Meanwhile, the reduced systemic exposure of Clop-AM in T2DM rats as compared to control rats was significantly reversed after antibiotic treatment, accompanied with the decreased expression of P-glycoprotein (P-gp) in small intestine, suggesting P-gp-based Clop absorption might be promoted, consequently making more Clop available for Clop-AM formation. Interestingly, fecal microbiome analysis exhibited the reduced microbial amount and the altered microbial composition in antibiotic-treated T2DM rats. Especially, there was an inconsistent change of P-gp levels between T2DM rats and SW480 cells after antibiotic treatment, suggesting antibiotic-induced microbiome depletion, not the direct role of antibiotics is associated with the enhanced Clop-AM plasma exposure in T2DM rats. Conclusion and Implication: The findings show that gut microbiota modulation is an effective therapeutic strategy to enhance Clop-AM generation under T2DM conditions.

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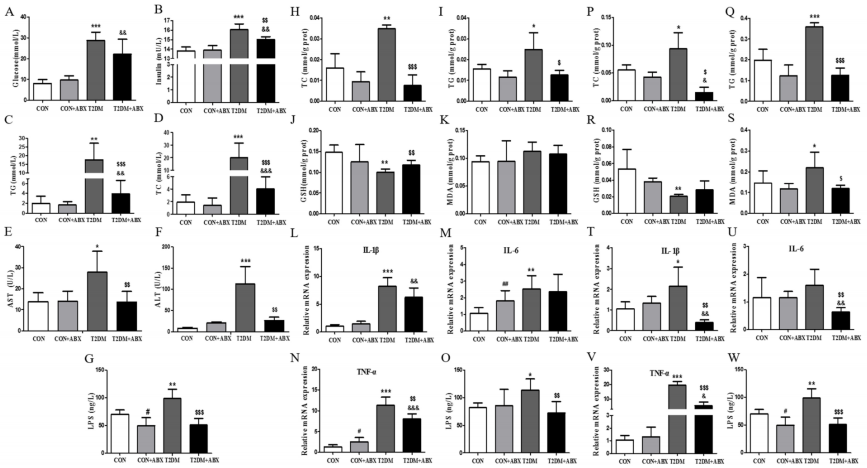

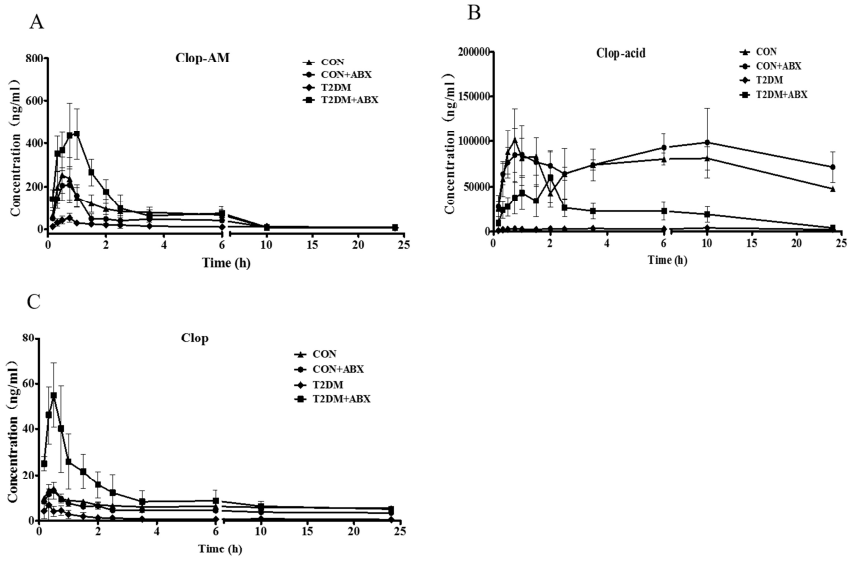

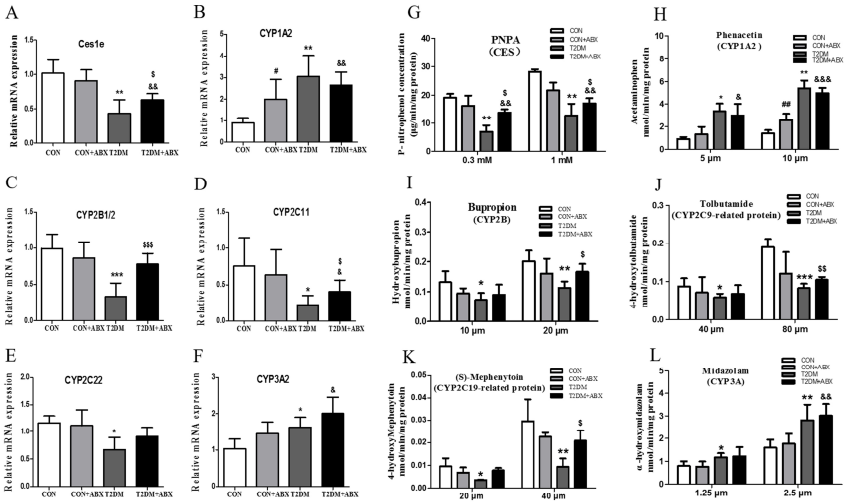

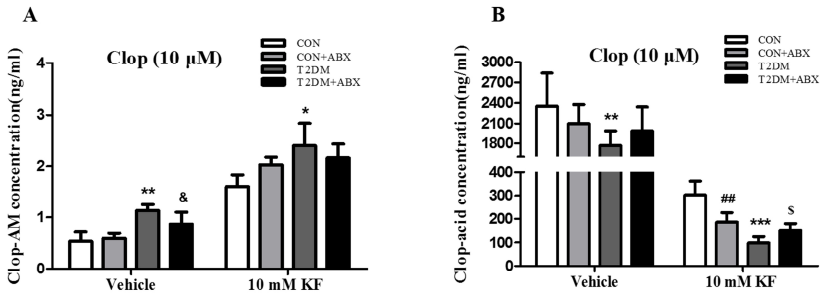

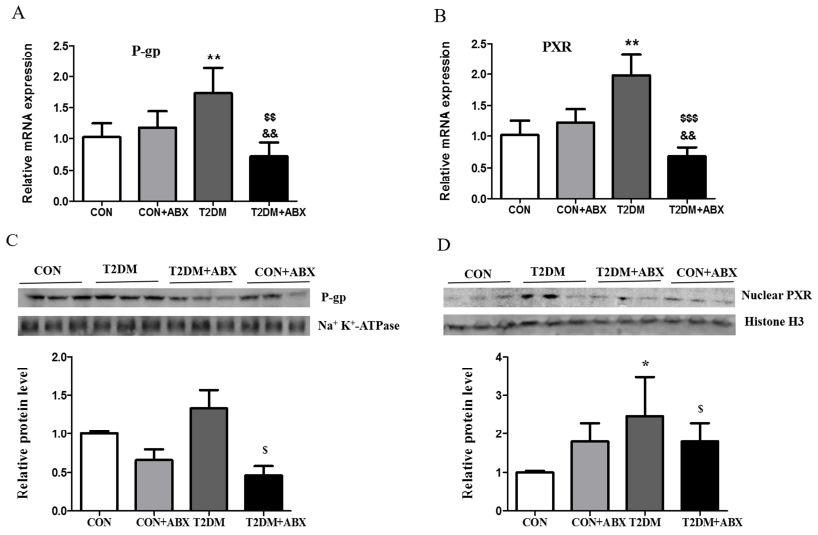

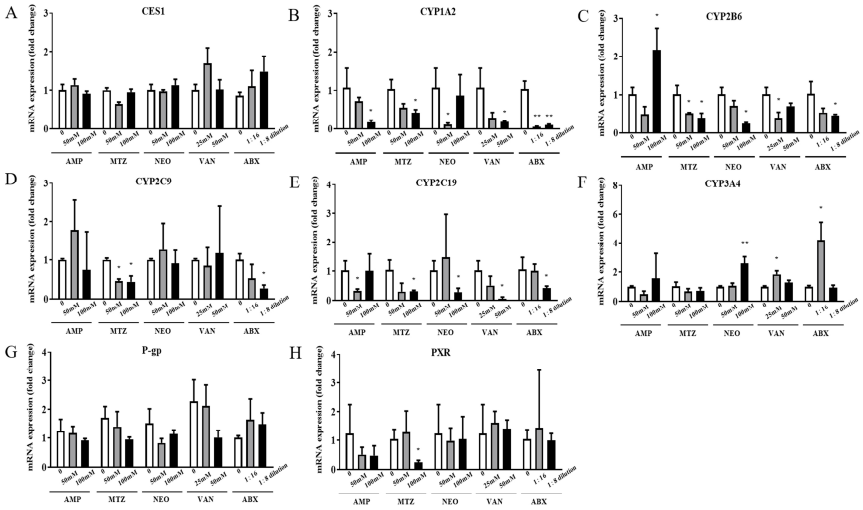

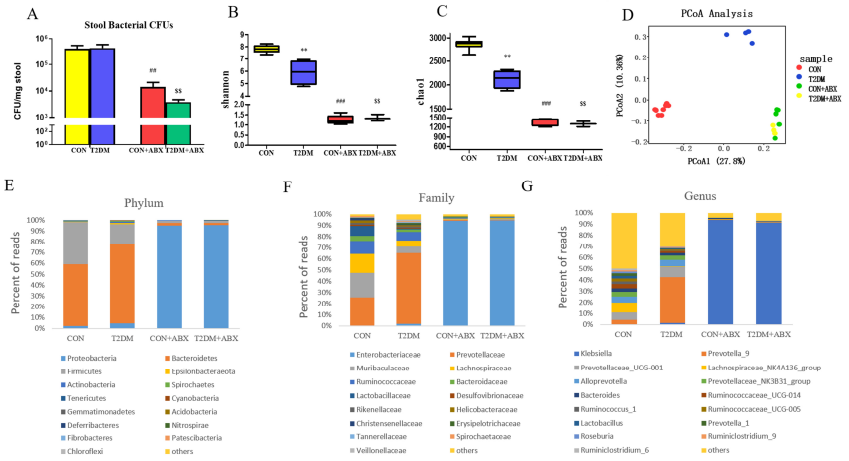

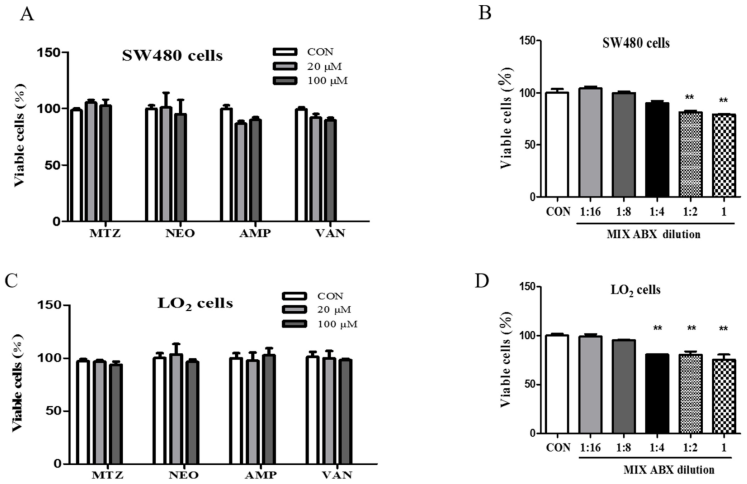

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