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Diabetes Treatment Drug Sitagliptin Exerts Strong Inhibition towards the Activity of UDP-Glucuronosyltransferases (UGTs)

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SUMMARY. **Sitagliptin is clinically employed with a proper diet to control high level of sugar in blood. This study aims to evaluate the effect of sitagliptin on the activity of important phase II drug-metabolizing enzymes (DMEs) UDP-glucuronosyltransferases (UGTs) isoforms. *In vitro* recombinant UGTs-catalyzed glucuronidation of 4-methylumbelliferone (4-MU) was used as the probe reaction to determine the effect of sitagliptin on UGTs. At 100 μM of sitagliptin, the activity of UGT1A1, 1A3, 1A6, 1A7, 1A9, and 2B7 was not significantly influenced; 100 μM of sitagliptin activated approximately 40% activity of UGT1A8 ($p < 0.01$) and 500% activity of UGT1A10 ($p < 0.01$). Due to the significant contribution of UGT1A8 and UGT1A10 towards the metabolism of many oral administered drugs, the potential drug-drug interaction between sitagliptin and the clinical drugs undergoing UGT1A8 and UGT1A10-catalyzed glucuronidation metabolism is possible.**

RESUMEN. La sitagliptina se emplea clínicamente con una dieta adecuada para controlar el alto nivel de azúcar en la sangre. Este estudio tiene como objetivo evaluar el efecto de la sitagliptina sobre la actividad de importantes enzimas metabolizadoras de fármacos (DME) de la fase II, isoformas de UDP-glucuronosiltransferasas (UGT). La glucuronidación catalizada por UGTs recombinantes *in vitro* de 4-metilumbeliferona (4-MU) se usó como la reacción sonda para determinar el efecto de la sitagliptina sobre las UGT. Con 100 μM de sitagliptina la actividad de UGT1A1, 1A3, 1A6, 1A7, 1A9 y 2B7 no se vio significativamente afectada; 100 μM de sitagliptina activaron aproximadamente 40% de la actividad de UGT1A8 ($p < 0.01$) y 500% de actividad de UGT1A10 ($p < 0.01$). Debido a la importante contribución de UGT1A8 y UGT1A10 al metabolismo de muchos fármacos administrados por vía oral, es posible la interacción fármaco-fármaco entre sitagliptina y los fármacos clínicos que experimentan el metabolismo de glucuronidación catalizada por UGT1A8 y UGT1A10.

KEY WORDS: diabetes mellitus (DM), drug-drug interaction (DDI), sitagliptin, UDP-glucuronosyltransferases (UGTs).

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