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RITONAVIR CAUSES HYPERTRIGLYCERIDAEMIA IN APOE*3-LEIDEN TRANSGENIC MICE BY IMPAIRING TRIGLYCERIDE CLEARANCE

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OBJECTIVES: The protease inhibitor ritonavir (RTV) increases plasma triglycerides (TG) both in humans and in mice. Our aim was to determine the mechanism underlying the RTV-induced hypertriglyceridaemia in APOE*3- Leiden transgenic mice which have a human-like lipoprotein profile.

METHODS: Female APOE*3-Leiden transgenic mice were fed a western-type diet with or without RTV added (35 mg/kg body weight/day).

RESULTS: After administration of RTV for 3 weeks, plasma TG increased from 2.7 ±0.6 to 5.3 ±1.9 mM ($P<0.01$), which was specific for VLDL. We first determined whether increased production of VLDL-TG could be the cause of the increased plasma TG. However, when compared with untreated mice, hepatic VLDL-TG production was not changed (138.5 ±41.2 vs 177.4 ±59.9 μmol TG/kg/h in controls; $P>0.05$). Interestingly, compared with control animals, RTV caused a 2.5-fold increased postprandial TG response upon an intragastric olive oil load, which suggests impaired TG clearance (5.0 ±2.5 vs 2.0 ±1.1 mM at 2 h after gavage; $P<0.05$). Indeed, clearance of intravenously injected [³H]TG-labelled VLDL-like emulsion particles was decreased in RTV-treated mice compared with untreated controls ($t_{1/2}$ 19.3 ±10.5 vs 5.0 ±1.3 min; $P<0.05$).

CONCLUSION: From these data, we conclude that RTV causes hypertriglyceridaemia by impairing plasma TG clearance rather than by stimulating hepatic VLDL-TG production.

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