Miyawaki I, Pharmaceut Anal Acta 2013, 4:2
http://dx.doi.org/10.4172/2153-2435.S1.017

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3rd International Conference and Exhibition on
Pharmaceutics & Novel Drug Delivery Systems
April 08-10, 2013 Hilton Chicago/Northbrook, USA

The effects of Clobazam treatment in rats on the expression of genes and proteins encoding glucronosyltransferase 1a/2b (UGT1a/2b) and multidrug resistance-associated protein-2 (MRP2), and development of thyroid follicular cell hypertrophy

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Clobazam (CLB) is known to increase hepatobiliary thyroxine (T_4) clearance in Sprague-Dawley (SD) rats, which results in hypothyroidism followed by thyroid follicular cell hypertrophy. However, the mechanism of the acceleration of T4-clearance has not been fully investigated. In the present study, we tried to clarify the roles of hepatic UDP-glucronosyltransferase (UGT) isoenzymes (UGT1A and UGT2B) and efflux transporter (multidrug resistance-associated protein-2; MRP2) in the CLB-induced acceleration of T_4-clearance using two mutant rat strains, UGT1A-deficient mutant (Gunn) and MRP2-deficient mutant (EHBR) rats, especially focusing on thyroid morphology, levels of circulating hormones (T_4 and triiodothyronine (T_3)) and thyroid-stimulating hormone (TSH), and mRNA or protein expressions of UGTs (Ugt1a1, Ugt1a6, and Ugt2b1/2) and MRP2 (Mrp). CLB induced thyroid morphological changes with increases in TSH in SD and Gunn rats, but not in EHBR rats. T_4 was slightly decreased in SD and Gunn rats, and T_3 was decreased in Gunn rats, whereas these hormones were maintained in EHBR rats. Hepatic Ugt1a1, Ugt1a6, Ugt2b1/2, and Mrp2 mRNAs were upregulated in SD rats. In Gunn rats, UGT1A mRNAs (Ugt1a1/6) and protein levels were quite low, but UGT2B mRNAs (Ugt2b1/2) and protein were prominently upregulated. In SD and Gunn rats, MRP2 mRNA and protein were upregulated to the same degree. These results suggest that MRP2 is an important contributor in development of the thyroid cellular hypertrophy in CLB-treated rats, and that UGT1A and UGT2B work in concert with MRP2 in the presence of MRP2 function to enable the effective elimination of thyroid hormones.

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