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Metabolic Reprogramming and Impaired Liver Metabolism in Hyperinsulinemic male LEW.1WR1 rats.

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Abstract

Metabolic diseases, including insulin resistance and fatty liver disease, are closely intertwined through shared metabolic disruptions. This study investigates early metabolic changes in LWE.1WR1 male rats, an insulin-resistant, hyperinsulinemic strain predisposed to metabolic dysfunction. Despite the absence of overt diabetes, these animals displayed early hepatic abnormalities indicative of metabolic dysfunction-associated steatotic liver disease (MASLD), suggesting a subclinical progression of liver pathology. Proteomic analysis of liver tissue revealed significant reductions in mitochondrial proteins and oxidative phosphorylation components, along with altered expression in pathways regulating branched-chain fatty acid metabolism and beta-oxidation. UBD/FAT10, a stress-response gene linked to inflammation and metabolic imbalance, was notably overexpressed. These changes suggest impaired hepatic energy regulation and lipid handling, both of which are cardinal features of metabolic syndrome. Histological findings from complementary studies confirmed hepatic steatosis, Mallory-Denk body formation, and fibrosis in 23-week-old LEW.1WR1 rats under a standard diet. The convergence of liver dysfunction, insulin resistance, and increased adiposity strongly supports this strain as a robust model of early metabolic diseases. These findings demonstrate that LEW.1WR1 rats exhibit intrinsic mitochondrial dysfunction and early liver damage independent of dietary extremes or diabetes onset. The model offers critical insights into the pathophysiological onset of metabolic disease and the molecular disruptions that precede clinical manifestation.