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Research Article

Impacts of Circadian Gene *Period2* Knockout on Intestinal Metabolism and Hepatic Antioxidant and Inflammation State in Mice

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The period circadian regulator 2 (*Per2*) gene is important for the modulations of rhythmic homeostasis in the gut and liver; disruption will cause metabolic diseases, such as obesity, diabetes, and fatty liver. Herein, we investigated the alterations in intestinal metabolic and hepatic functions in *Per2* knockout ($Per2^{-/-}$, KO) and wild-type ($Per2^{+/+}$, WT) mice. Growth indices, intestinal metabolomics, hepatic circadian rhythms, lipid metabolism, inflammation-related genes, antioxidant capacity, and transcriptome sequencing were performed after euthanasia. Data indicated that KO decreased the intestinal concentrations of amino acids such as γ-aminobutyric acid, aspartic acid, glycine, L-allothreonine, methionine, proline, serine, and valine while it increased the concentrations of carbohydrates such as cellobiose, D-talose, fucose, lyxose, and xylose compared with WT. Moreover, the imbalance of intestinal metabolism further seemed to induce liver dysfunction. Data indicated that *Per2* knockout altered the expression of hepatic circadian rhythm genes, such as *Clock*, *Bmal1*, *Per1*, *Per3*, *Cry1*, and *Cry2*. KO also induced hepatic lipid metabolism, because of the increase of liver index and serum concentrations of low-density lipoprotein, and the upregulated expression of *Pparα*, *Cyp7a1*, and *Cpt1*. In addition, KO improved hepatic antioxidant capacity due to the increase activities of SOD and GSH-Px and the decrease in concentrations of MDA. Lastly, KO increased the relative expression levels of hepatic inflammation-related genes, such as *Il-1β*, *Il-6*, *Tnf-α*, *Myd88*, and *Nf-κB p65*, which may potentially lead to hepatic inflammation. Overall, *Per2* knockout induces gut metabolic dysregulation and may potentially trigger alterations in hepatic antioxidant and inflammation responses.

1. Introduction

Circadian rhythms are defined as the cyclical changes in physiology, metabolism, behavior, and circulation according to a 24 h cycle in the life of mammals regulated by the periodic expression of a series of circadian clock genes [1, 2]. At present, many circadian clock genes have been identified in animals including period circadian clock 1/2/3 (*Per1/2/3*), cryptochrome 1/2 (*Cry1/2*), brain and muscle ARNT-like 1 (*Bmal1*), and circadian locomotor output cycle kaput (*Clock*) [3, 4]. A central circadian clock located in the suprachiasmatic nucleus (SCN) coordinates the oscillation of the peripheral circadian clock, while the intrinsically photosensitive retinal ganglion cells (ipRGCs) send light signals into SCN to guide the central clock to periodically oscillate and output rhythmic behaviors consistent with daily changes [5]. The circadian clock is produced by the transcriptional-translational feedback loops (TTFLs) of circadian genes [6,