



The Role of Carnitine Orotate Complex in Fatty Liver

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Carnitine (β -hydroxy- γ -trimethylammonium butyrate), a natural nutrient, primarily acts as an essential cofactor for the mitochondrial β -oxidation of fatty acids by promoting the transport of long-chain fatty acids across the mitochondrial membrane in the form of acyl carnitine esters [1]. The products of β -oxidation are used in the tricarboxylic acid cycle to produce adenosine triphosphate as a form of stored energy. This mechanism is important in diseases related to mitochondrial fatty acids oxidation, in which fatty acyl-coenzyme A accumulate in metabolic organs [2]. Moreover, carnitine protects cells against reactive oxygen species induced by mitochondrial stress or DNA damage, which leads to inhibition of mitochondria-dependent apoptosis [3,4].

Orotate, a precursor in biosynthesis of pyrimidines, is found abundantly in milk produced by cows and other dairy products [5]. Dihydroorotate dehydrogenase, an integral protein in the mitochondrial inner membrane, catalyzes the oxidation of dihydroorotate to orotate, which is then converted to uridine monophosphate by uridine monophosphate synthase [6]. Moreover, orotate is well known to be remarkably increased in many congenital diseases associated with defects of the urea cycle or arginine metabolism [7]. Although orotate has a protective role in cardiovascular diseases [8,9], there has been no study showing the precise mechanism of orotate for the attenuation of metabolic diseases.

In the article titled “Carnitine orotate complex ameliorates insulin resistance and hepatic steatosis through carnitine acetyltransferase pathway,” Hong and Lee [10] investigated whether carnitine-orotate complex attenuates high-fat diet-induced steatosis and insulin resistance in mice. Consistent with their previous investigation using the carnitine-orotate complex [11],

the authors showed that carnitine-orotate complex inhibited weight gain and fat volume gain without food intake, as well as improved insulin sensitivity and glucose tolerance in high-fat diet-fed mice. They also found a protective effect of carnitine-orotate complex on liver injury and hepatic fat accumulation in mice with diet-induced obesity. Intriguingly, carnitine-orotate complex increased the expressions of sirtuin 1, peroxisome proliferator-activated receptor- γ coactivator 1- α , and nuclear respiratory factor 1 in the liver of the mice fed with a high-fat diet, which may contribute to the improvement of hepatic steatosis through enhancing fatty acid β -oxidation in the liver. To further define the mechanism of carnitine-orotate complex, Hepa-1c1c cells were treated with carnitine-orotate complex to observe the expression of carnitine acetyltransferase (CrAT). Knockdown of CrAT remarkably reduced carnitine-orotate complex-mediated increases in phosphorylated AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- α (PPAR α) in Hepa-1c1c cells. Therefore, they suggest that CrAT is a key factor for carnitine-orotate complex-induced metabolic improvement in mice.

Based on previous studies [10,11], carnitine-orotate complex is regarded as one of the most promising drugs for preventing insulin resistance and metabolic liver disease. Hepatic steatosis progresses to hepatocyte injuries and induces initiation of inflammation, which activates liver-resident immune cells. In other words, the liver is an immunologic organ because of the enrichment of diverse types of immune cells, which are involved in the pathogenesis of fatty liver and advance liver diseases [12]. Therefore, the role of carnitine-orotate complex on the population and activation of hepatic immune cells should be elucidated in the development of non-alcoholic steatohepa-

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titis and liver fibrosis. Moreover, based on the immunomodulatory roles of hepatic stellate cells and bidirectional interactions between hepatic stellate cells and immune cells [12-14], further investigations are needed to identify whether carnitine-orotate complex regulates the activation of hepatic stellate cells. On the other hand, emerging investigations indicated that mitochondrial unfolded protein response and mitokine networks not only inhibit the progression of fatty liver [15,16], but also ameliorate liver fibrosis and injury in mice [17]. Thus, it would be interesting to determine how carnitine-orotate complex affects mitochondrial unfolded protein response and mitokine production, which may regulate the attenuation of fatty liver and advanced liver disease.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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