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Long-chain bases from sea cucumber inhibits renal fibrosis and apoptosis in type 2 diabetic mice

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ABSTRACT

Long-chain bases (LCBs) from sea cucumber exert antineoplastic, antihyperglycemia and anti-inflammatory activities. However, their renoprotective effects are undiscovered. Here, we investigated the effects of LCBs on protection against type 2 diabetic nephropathy in mice. Results showed that LCBs attenuated renal dysfunction through the reductions of urine glucose and albumin-to-creatinine ratio, which are associated with the decreases in serum lipids, body weight, insulin resistance, and renal inflammation. LCBs inhibited tubular atrophy, aglomerular lipid droplet, and glomeular basement membrane thickening, and promoted brush border density, suggesting their effects on protection against renal injury. LCBs mitigated renal fibrosis through blocking transforming growth factor-β/Smad signaling. Renal apoptosis was suppressed by LCBs administration through activation of PI3K/Akt and ERK pathways. These results demonstrate that LCBs have significantly renoprotective effects *via* declining the progression of renal fibrosis and apoptosis. These will provide a significant implication for LCBs utilization as functional foods against type 2 diabetic nephropathy.

1. Introduction

Type 2 diabetes mellitus is a worldwide epidemic associated with high morbidity. More than 90% of diabetic patients belong to type 2 diabetes, and it is predicted that worldwide diabetes prevalence will reach up to 550 million by 2030 (Shaw, Sicree, & Zimmet, 2010; Yoon et al., 2006). Diabetic nephropathy (DN) is one of the most common and serious complications of type 2 diabetes mellitus at a ratio of approximately 40% (Wang, Zhao, Yang, Wang, & Kuang, 2016). Furthermore, DN is the leading cause of significant mortality in type 2 diabetic patients, as 30%-45% of the patients eventually develop end-stage renal disease (ESRD) (Pan et al., 2014; Rhee et al., 2017). It is characterized by excessive extracellular matrix (ECM) with glomerular and tubular basement membrane (GBM) thickening, tubulointerstitial fibrosis, and renal inflammation, resulting in severe nephropathy appearance such as a slowly increasing proteinuria and a gradually decreasing renal function. Renal fibrosis is a final common pathologic feature in the later stage of disease. Transforming growth factor β (TGF-β)/Smad signaling-mediated ECM accumulation, including fibronection, directly induces fibrotic lesions (Lan & Chung, 2012). Therefore, inhibition of TGF-β/Smad pathway has become a promising therapeutic candidate for precaution of DN. Significant apoptosis occurs in the glomeruli and renal tubules from the early stage of nephropathy to especially ESRD (Verzola et al., 2007). Renal apoptosis is a hallmark of DN and a reliable indicator of the disease progression (Brezniceanu et al., 2010). Phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB/Akt) signaling is proved to be widely expressed in eukaryotes and plays essential roles in growth, differentiation, proliferation and survival (Cantley, 2002). Meanwhile, PI3K/Akt pathway is also involved in renal apoptosis of type 2 diabetic mice (Huang et al., 2016). Mitogen-activated protein kinase (MAPK) pathway is another important pathological mechanism of renal apoptosis. Extracellular signal-regulated

Abbreviations: Akt, protein kinase B; DN, diabetic nephropathy; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; ESRD, end-stage renal disease; GBM, glomerular basement membrane; HFD, high fat diet; H&E, hematoxylin and eosin; IITT, intraperitoneal insulin tolerance test; IL-1β, interleukin-1β; LCBs, long-chain bases; OGTT, oral glucose tolerance test; PI3K, phosphoinositide 3-kinase; qRT-PCR, quantitative real-time polymerase chain reaction; STZ, streptozotocin; TGF-β1, transforming growth factor-β1; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; UACR, urinary albumin-to-creatinine ratio

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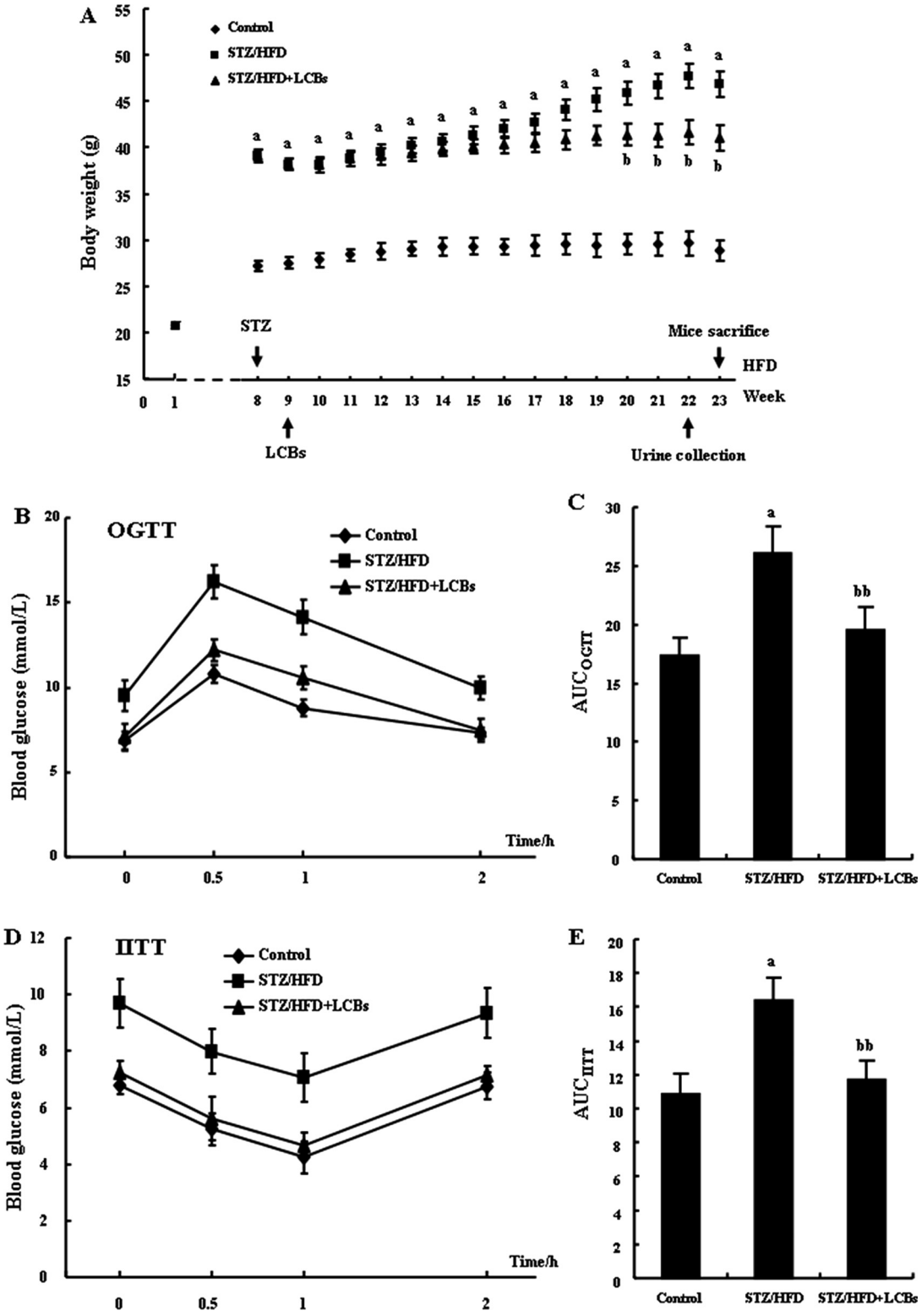

Fig. 1. Effects of LCBs on body weight, oral glucose tolerance test (OGTT) and intraperitoneal insulin tolerance test (IITT). Type 2 diabetes were induced by intraperitoneal administration of a signal low dose of streptozotocin (STZ, 40 mg/kg) at Week 8 in high fat diet (HFD)-feeding mice. Diabetic mice were treated with an oral dose of LCBs (10 mg/kg) at Week 9. OGTT: overnight fasting blood at 0, 0.5, 1, and 2 h after intragastrically given 2 g glucose per kg body weight was collected from the caudal vein at 22 weeks for measuring blood glucose level to calculate AUC_{OGTT}. IITT: overnight fasting blood at the indicated time points after intraperitoneal injection of 0.5 U insulin per kg body weight was collected from the caudal vein at 22 weeks for measuring blood glucose level to calculated AUC_{IITT}. A, Body weight and animal experimental design ($n = 12$); B, blood glucose level at indicated time points in OGTT; C, AUC_{OGTT}; D, blood glucose level at indicated time points in IITT; E, AUC_{IITT}. $^{a}p < .01$ compared with control mice; $^{b}p < .05$, $^{bb}p < .01$ compared with STZ/HFD mice.

kinase 1/2 (ERK1/2) is one of the crucial kinase in MAPK family, and phosphorylated ERK1/2 triggered inactivation of caspase 3 through regulation of Bax and Bcl-2 (You et al., 2017).

Increasing attentions have been attracted in the paper on long-chain bases (LCBs), also namely sphingoid bases, the simplest members in the family glycosphingolipids. Current research has proved that LCBs