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论著

过氧化物酶体增殖物激活受体β亚型激动剂GW501516对胰岛素抵抗模型小鼠的胰岛素增敏作用

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摘要 目的 在长期（4个月）高脂高糖饮食诱导的胰岛素抵抗小鼠模型上，评价过氧化物酶体增殖物激活受体β(PPARβ)亚型激动剂GW501516对胰岛素抵抗的改善作用，并对可能的相关机制进行探讨。方法 C57BL/6J小鼠采用高脂高糖饮食（35%脂肪，30%麦芽糖）诱导4个月，待产生明显的糖脂代谢紊乱。实验分为正常对照、饮食导致的肥胖（DIO）模型与DIO模型+GW501516(10 mg·kg^{-1}·d^{-1}) 给药组。隔天监测体重与进食量情况，以葡萄糖氧化酶法检测血糖，并进行口服葡萄糖耐量试验和血脂(甘油三酯、总胆固醇和高密度脂蛋白)含量的检测。以组织学方法检测肝脏异位脂积聚及病理变化情况。为确证其相关作用机制，采用RT-PCR方法检测骨骼肌内PPARβ下游糖脂代谢靶基因的表达。结果 GW501516有效改善模型小鼠的胰岛素抵抗，显著降低口服糖耐量曲线下面积〔DIO模型组，(32.4±4.6) mmol·h·L^{-1}，DIO+GW501516组，(23.4±2.5) mmol·h·L^{-1}，n=7～8，P<0.05〕，降低空腹血糖，增加血清高密度脂蛋白含量，减轻模型小鼠的肝脂肪变性。此外，RT-PCR结果表明，骨骼肌卡尼汀(肉碱)软脂酰转移酶1b，解偶联蛋白(UCP)2，UCP3明显上调，同时葡萄糖转运蛋白也明显上调。结论 GW501516显著改善模型小鼠的胰岛素抵抗，恢复其空腹血糖值，降低肝脏内异位脂积聚，其治疗作用机制可能与①促进骨骼肌内脂肪酸氧化和能量的解偶联，②促进骨骼肌内的糖摄取有关，提示PPARβ可能是胰岛素抵抗及代谢综合征的有效治疗靶标。

关键词 过氧化物酶体增殖物激活受体β 胰岛素抵抗 GW501516 代谢综合征

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Peroxisome proliferator-activated receptor β agonist, GW501516, ameliorates insulin resistance in glucose intolerant mouse model

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Abstract

AIM The effects of GW501516, a peroxisome proliferator-activated receptor β (PPARβ) agonist, in long term diet induced obesity (DIO, high fat and maltose diet for 4 months) mice were evaluated, and the efficacy of GW501516 against insulin resistance and the involved mechanism was investigated. **METHODS** Mice were divided into 3 groups: normal control, DIO model and DIO model+GW501516. GW501516 (10 mg·kg^{-1}·d^{-1}) was administered by ig once a day for 14 d. During the treatment, body weight and food intake were monitored every other day. The oral glucose tolerance test, and the serum biochemical parameters including the serum triglyceride, total cholesterol and high density lipoprotein cholesterol (HDL-C) levels were measured according to the specifications. To confirm the GW501516-mediated PPARβ activation, the mRNA levels of downstream genes related to glucose, lipid metabolism and energy expenditure was measured. **RESULTS** GW501516 treatment effectively improved the glucose intolerance, increased the area under the glucose curves〔DIO model, (32.4±4.6) mmol·h·L^{-1} compared with DIO model+GW501516, (23.4±2.5) mmol·h·L^{-1}, n=7-8, P<0.05〕, normalized the fasted blood glucose, and increased serum HDL-C level, besides, histological analysis revealed the decreased hepatic lipid accumulation and hypertrophy of hepatocyte in DIO mice. Moreover, RT-PCR results indicated that carnitine palmitoyltransferase 1b, uncoupling protein 2, uncoupling protein 3 and glucose transport protein 4 were all upregulated. **CONCLUSION** GW501516 significantly ameliorates glucose intolerance, decreases fasted blood glucose and hepatic steatosis, which might be related to ① the enhancement of fatty acid oxidation and energy uncoupling in muscle, and ② the improvement of insulin-stimulated glucose transportation in skeletal muscle in the long term DIO mice.

Key words peroxisome proliferator-activated receptor β insulin resistance GW501516 metabolic syndrome

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