P-0439-Expression and mechanism of FGF21 in white adipose tissue of obese type 2 diabetic rats induced by liraglutide

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Introductions:

Fibroblast growth factor (FGF-21), an endocrine member of the FGF superfamily ,is a new adipokine as regulator of energy homeostasis, especially in control of body weight and lipid homeostasis . FGF21 also increase insulin sensitivity and improve glucose tolerance. Liraglutide is a glucagon-like peptide-1 analogues that stimulates insulin secretion and improves β -cell function, ameliorate blood glucose and weight loss. However, it is not clear whether liraglutide achieves its glucose and lipid lowering effect by increasing FGF21 expression and activating AMPK pathway in white adipose tissue and cells from obese rat models of type 2 diabete mellitus (T2DM).

Aims:

1. To determiner the relationship between serum FGF-21 levels and biochemical indices in T2DM male SD rats. 2. To study the effect of liralutide on FGF-21 expression and AMPK pathway in WAT from T2DM rats to explore the role of FGF-21 in reducing weight loss and lipid synthesis.

Methods :

1. Animal experiment: Male SD rats were subjected to a standard control diet (CON) or high-fat diet (HFD) for 16 weeks, then the HFD group was introperitoneally injected with 30mg/kg streptozotocin to construct type 2 diabetes mellitus model. Then half rats of type 2 diabetes mellitus were injected with liraglutide (DM+LRG, 0.4mg/kg/d, two times one day) for another 8 weeks. The pathological changes in white adipose tissue were detected by H&E staining. FGF21 were assessed by RT-PCR, immunohistochemistry and Western blot respectively. RAW264.2 cells were cultivated and treated with mixture of glucose and palmitic acid, the mRNA and protein expression of FGF21 and AMPK were assessed by RT-PCR and Western blot respectively.

Results:

1. Combination of high-fat diet and strepzotocin sucessfully constructed a type 2 diabetes mellitus rat model, accompliced with insulin resistance, reduced FGF21 in serum and WAT, and AMPK signaling in WAT, and liraglutide treatment markedly ameliorate these response . 2.In High glucose high f (HGHP) group, it can significantly reduce the level of fibroblast growth factor-21 in RAW264.7 cells, while liraglutide can reverse this effect, showing a dose-dependent effect, and may regulate downstream AMPK signaling pathway through GLP-R. Realtime RT-PCR results showed that the expression of fibroblast growth factor-21 in liraglutide group was higher than that in high glucose and high fat group, and showed a dose-dependent effect. In GLP-1R inhibitor experiment, liraglutide showed a dose-dependent expression of fibroblast growth factor-21 in liraglutide group. The protein expression of the cells was improved after the inhibitor action

Table 1

Group	TC	TG	HDL-C	ALT	AST
CON	1 $\pm$ 0.36	0.39 $\pm$ 0.14	1.08 $\pm$ 0.21	46.25 $\pm$ 20.85	92.75 $\pm$ 26.91
DM	1.49 $\pm$ 0.4 [#]	0.76 $\pm$ 0.78 [#]	1.09 $\pm$ 0.25	93.33 $\pm$ 36.12 [#]	101 $\pm$ 23.98 ^{##}
DM+L	1.50 $\pm$ 0.03	0.56 $\pm$ 0.23	1.3 $\pm$ 0.12 ^{**}	70.95 $\pm$ 15.88 [*]	70.95 $\pm$ 12.73 ^{**}

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Fig 2 利拉鲁肽对大鼠血清 FGF21 水平的影响

Conclusions :

Those findings demonstrate an additive effect of HFD on insulin resistance and liraglutide significantly improved insulin sensitivity in adipose tissues, maybe via increasing FGF21 and activating AMPK pathway