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论著

阻断肾素血管紧张素系统对长期高脂喂养胰岛素抵抗大鼠胰岛UCP2和GCLC表达的影响

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摘要 目的： 观察长期高脂喂养的胰岛素抵抗大鼠胰岛氧化应激机制以及阻断肾素血管紧张素系统（RAS）对其的影响，探讨RAS与氧化应激、糖代谢之间的关系。方法: 雄性Wistar大鼠分为正常饲养组（NC组）、高脂饲养组（HF组）、高脂+培哚普利组（FP组）、高脂+替米沙坦组（FM组），后2组大鼠喂养16周后分别以培哚普利2 mg·kg-1·d-1（FP组，n=15）和替米沙坦10 mg·kg-1·d-1（FM组，n=15）干预，8周后行正常血糖高胰岛素钳夹试验评估外周胰岛素抵抗程度，行静脉葡萄糖耐量试验检测胰岛β细胞功能 ，以RT-PCR检测γ谷氨酰半胱氨酸连接酶的催化亚基（GCLC）的表达，以免疫组化法检测胰岛局部线粒体解偶联蛋白2（UCP2）水平，以比色法测定胰腺组织丙二醛（MDA）的含量。结果: 与正常饲养组相比，高脂饲养组的葡萄糖输注率（GIR）降低了31.8%,胰岛GCLC表达降低了31.5% ，局部UCP2相对浓度增加了17.0%,胰腺MDA含量增加了0.46倍（均P<0.01），0-10 min胰岛素曲线下面积（AUC10-10）为(271.8±33.8)vs（282.7±29.8）mIU·L-1·min-1，糖刺激后早期胰岛素分泌降低，但无显著差异；培哚普利或替米沙坦干预后，GIR分别增加了27.8%和30.8%，胰岛GCLC表达分别增加了26.6%和26.6% ，局部UCP2相对浓度分别下降了13.0%和15.6%，胰腺MDA含量分别下降了18%和20%（均P<0.01），FP、FM组之间无显著差异。结论: 阻断RAS可以改善高脂喂养大鼠的胰岛素抵抗和胰岛β细胞分泌功能，其机制可能为通过下调胰岛局部UCP2和上调GCLC的表达，减轻氧化应激损伤，从而保护胰岛β细胞功能。

关键词 肾素-血管紧张素系统； 胰岛素抵抗； 解偶联蛋白2； 谷氨酰半胱氨酸连接酶的催化亚基

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Effects of blockade of rennin-angiotensin system on expression of uncoupling protein-2 and catalytic subunit of glutamylcysteine ligase in pancreatic islets in rats with insulin resistance and long-term high-fat diet

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Abstract

<FONT face=Verdana>AIM: To study the mechanism of oxidative stress in rats characteristic of insulin resistance with long-term high-fat diet and to observe the effects of rennin-angiotensin system (RAS) blockade on the functions of RAS, oxidative stress and glucose metabolism.METHODS: Male Wistar rats were randomly divided into 4 groups: normal chow group (NC), high-fat-chow group (HF), perindopril treated group (FP, perindopril and high-fat-chow), and telmisartan treated group (FM, telmisartan and high-fat-chow). At the end of 16 week experiment, the last two groups were treated with perindopril 2 mg·kg-1·d-1 and telmisartan 10 mg·kg-1·d-1, respectively. After 8 week intervention, the glucose infusion rate (GIR) was measured by using euglycemic hyperinsulinemia clamp to evaluate the peripheral insulin resistance. Islet function of all the animals was evaluated by the intravenous glucose tolerance test. The mRNA expression levels of catalytic subunit of glutamylcysteine ligase (GCLC) in the islets were detected by RT-PCR. Immunohistochemical technique with qualitative and (or) quantitative analysis was applied to determine the expression of uncoupling protein-2 (UCP2) in the islets. The contents of malonaldehyde in the pancreatic tissue were determined by chromatometry.RESULTS: Compared to NC group, GIR in HF group was

decreased by 31.8%, the relative expression of local GCLC was decreased by 31.5%，the relative content of UCP2 was increased by 17.0% (all P<0.01). The area under the curve of blood insulin between 0 and 10 minutes (AUCI0-10) was (271.8±33.8) vs (282.7±29.8) mIU·L-1·min-1, glucose-stimulated early insulin secretion was decreased, but there was no significant difference. Compared to HF group, the GIR of FP and FM groups was increased by 27.8% and 30.8%, respectively. The relative expression of local GCLC was increased by 26.6% and 26.6%, respectively, the relative content of UCP2 was decreased by 13.0% and 15.6%, respectively (all P<0.01). No significant difference between group FP and FM was found.CONCLUSION: Blockade of rennin-angiotensin system improves insulin resistance and pancreatic islet β-cell function in rats with long-term high-fat diet. The β-cell function may be protected by down-regulating the expression of uncoupling protein-2 (UCP2), up- regulating the expression of catalytic subunit of glutamylcysteine ligase (GCLC) and attenuating oxidative stress.</FONT>

Key words Rennin-angiotensin system Insulin resistance Uncoupling protein-2 Catalytic subunit of glutamylcysteine ligase

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