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论著

无生长追赶SGA幼鼠生长激素和胰岛素受体后信号交联对话的研究

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摘要 目的：在生长激素（GH）和胰岛素（INS）共享受体后PI3K通路基础上探讨无生长追赶的出生低体重（NCU-SGA）幼鼠GH和INS抵抗的受体后机制，以及2者受体后信号通路的交联对话（cross-talk）。
方法:取4周龄NCU-SGA雄性大鼠，采用Western印记及免疫共沉淀技术分别测定NCU-SGA幼鼠在基础状态下、胰岛素激发以及先给予GH受体后信号通路JAK2阻滞剂AG490后再行胰岛素激发后（AG490+INS组）肝组织胰岛素受体底物-1（IRS-1）及其下游信号磷酸化Akt(p-Akt)的表达。
结果:（1）IRS-1信号表达： SGA鼠基础状态、INS激发后和AG490+INS组，3组间的IRS-1总蛋白及IRS-1磷酸化水平与正常对照组（C组）无显著差异（P＞0.05）。（2）p-Akt信号表达： C组基础状态时无p-Akt信号表达，INS刺激后表达明显增强。SGA鼠基础状态时p-Akt已有显著表达（慢性激活），INS刺激后表达较基础状态增加，但增殖显著低于正常对照组（P＜0.01）；AG490+INS组的p-Akt较JAK2未被阻断时明显增强（P＜0.01），但仍显著低于正常对照组（P＜0.01），提示GH的信号干扰了INS受体后IRS-1至Akt的信号转导。
结论:NCU-SGA幼鼠INS抵抗的发生与IRS-1-Akt通路受损有关，GH抵抗经GH和INS 2者受体后信号通路间的交联对话（cross-talk）使IRS-1至Akt间的信号转导解偶联,诱导和加重了INS抵抗；而PI3K-Akt可能是发生该解偶联的主要交汇点。

关键词 小于胎龄儿 大鼠 生长激素抵抗； 胰岛素抗药性； 信号转导

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Post-receptor signaling crosstalk between GH and insulin in non-catch-up growth rats born small for gestational age

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Abstract

<FONT face=Verdana>AIM:To investigate the post-receptor mechanism of growth hormone (GH) resistance and insulin (INS) resistance and their relationship in non-catch-up growth rats born small for gestational age (NCU-SGA), based on the post-receptor signalling cross-talk between GH and INS at PI3K signaling pathway.
METHODS:NCU-SGA rat model was developed by food restriction to pregnant dams. 4 weeks old male NCU-SGA rats were studied. Total and phosphate insulin receptor substrate-1(IRS-1) and its downstream signal Akt levels in liver tissue were measured by Western blotting or immunoprecipitation at baseline, post-stimulating of insulin, and pre-treatment with JAK2 (post-receptor signaling protein of GH) inhibitor AG490 then given insulin stimulation, respectively.
RESULTS: (1) Expression levels of total and phosphate IRS-1: No difference between NCU-SGA rats and normal control was observed (P>0.05). (2) Expression levels of Akt : At baseline, Akt was already activated in NCU-SGA rats compared to no Akt activation in normal control rats. However, post- stimulating of insulin, the increase level of phosphate Akt in NCU- SGA rats was remarkably lower than that in control rats (P<0.01). When pre-treatment with JAK2 inhibitor to block GH signaling pathway, the impaired Akt activity was significantly restored (P<0.01), which suggested that the signaling of GH uncouples signal transduction from IRS-1 to Akt in NCU-SGA rats.CONCLUSION:Insulin resistance is related to impaired IRS-1-Akt signaling pathway in NCU-SGA rats. GH resistance mediates and aggrevates INS resistance by uncoupling signal transduction from IRS-1 to Akt via signaling cross-talk at post-receptor level between GH and INS. PI3K/Akt may be the major site for this uncoupling.</FONT>

Key words Small for gestational age Rats Grow hormone resistance Insulin resistance Signal transduction

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